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ATHEROSCLEROSIS

Mark D. Altschule, M.D., *Guest Editor*

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Foreword

The relation of angina pectoris to coronary atherosclerosis was recognized almost two centuries ago; myocardial infarction (or at least coronary occlusion) was first recognized clinically a century and a quarter ago. Today both the diagnosis and treatment of the syndromes characterized mainly by cardiac pain are effected with a high degree of precision. Recent advances are due largely to the development of devices and techniques, the specific need for each of which was enunciated by clinicians charged with the care of patients. Today the technological advances that have been applied to the syndromes of coronary atherosclerosis have been outstandingly successful with respect to the cardiac arrhythmias, but less notably successful with respect to some of the other disorders. One purpose of the present volume is to summarize the latest and best diagnostic and therapeutic approaches.

It is evident, in general, that when a disease is easily and satisfactorily treated the pressure put on medical scientists to elucidate etiology and define preventive measures is relatively mild. On the other hand, when a disease is increasing in frequency—as coronary atherosclerosis clearly is—and when treatment of some of its manifestations is far from satisfactory, this pressure is likely to be both heavy and persistent. Accordingly the last few decades have seen a great amount of interest in the cause and prevention of coronary atherosclerosis. There have been consequent changes in the medical literature. One has been a change in volume; the massive literature on various aspects of the problem of prevention, including preventive treatment, has necessitated frequent reviews, such as the present volume, to give physicians a more or less current summary and evaluation of these writings. The second change in the medical literature bearing on coronary atherosclerosis has been an unfortunate propensity toward acceptance of the quick answer. However spectacular as a form of athletic prowess the leaping at conclusions may be, it does medicine no good and may do it great harm.

The too hasty acceptance of the dietary cholesterol-saturated fat hypothesis of atherosclerotic etiology is an example of this leaping at a conclusion. The support of this hypothesis has consisted of two main types of evidence, neither of them valid. One type of evidence is derived from experiments in which animals are fed absurdly large amounts of cholesterol, the species being chosen because of their susceptibility to this kind of poisoning, the nonsusceptible species being largely bypassed. In many experiments the animals have been made abnormal by manipulation of their hormonal status. However unsatisfactory these experi-

ments may be, they are made even more so – totally invalid, in fact – by what has long been known to chemists but almost totally ignored by experimental pathologists: cholesterol on exposure to air is quickly oxidized to a dozen or two other compounds, some of which may be highly toxic to blood vessels. These compounds have yet to be identified and then tested in animal experiments. At the moment the only reasonable conclusion as regards diet and atherosclerosis is that cholesterol in the foods of an ordinary diet has never been shown to be harmful, but that processing of food, now applied to most of the items in the American diet, probably changes some of it to substances toxic to blood vessel cells.

The second type of evidence used to support the dietary cholesterol-saturated fat hypothesis comprises statistical studies of the food habits of patients with coronary atherosclerosis, and of the effects of changes in their diets. The statistical studies have one common characteristic: they are never quite adequate. They all lead to the same conclusion, namely that despite vast expenditures of time, effort, and money, more work would have to be done to establish anything, except perhaps the fact that more work has to be done. The difficulties of working with populations of up to 5000 persons, when a cohort of perhaps 500,000 persons would be necessary to obtain statistically valid conclusions, have received technical discussion by a number of statisticians. One by Bauman (Medical Counterpoint, April 1972, p. 27) shows how having to work with numbers far smaller than are acceptable for statistical purposes forces those who conduct these studies to make assumptions that give neat mathematical data which unfortunately cannot be supported by statistical theory.

It is impossible to accept conclusions made from these studies and to justify making any more of them. Despite this, the notion that coronary atherosclerosis is caused by dietary intake of cholesterol-saturated fat has been given the status of official dogma in this country, to be disregarded at the threat of peril to one's life. It seems to me that the establishment of this dogma, whether accepted or not by individual physicians and their patients, represents dangers to medicine and health that are far more serious than not accepting it. Dissemination in the news media of the unproved and improbable notion as established fact is indefensible, and participation of physicians in such enterprises is unfortunate.

What then is the clinician to do? Under these circumstances he must turn (or return) to the basics. Although in general clinical observations are more likely to lead to advances in basic sciences than basic science studies are to lead to advances in clinical practice, when etiology is the question under investigation the basic science data must always have the dominant role. Accordingly when etiology is considered in the present volume, atherosclerosis is treated as what it is, namely, a biological phenomenon widely distributed in vertebrates, at least from the higher fishes upward in the phylum. Basic concepts and techniques of biology are here applied to the problem of the etiology of atherosclerosis, with results that the reader can evaluate for himself.

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Significance of Intimal Arterial Changes in Non-Human Vertebrates

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Studies of spontaneous vascular lesions in animals are important for several reasons. Conducted in a particular species, such as the work of Clarkson in pigeons,[5] Middleton in squirrel monkeys,[17] McGill in baboons,[15] Moreland in miniature swine,[18] and Malinow in howler monkeys,[16] these studies provide baseline data for comparison with experimentally induced arterial lesions in that species. Conducted in a large number of species, such as the work of Fox[9] and Ratcliffe[20] at the Philadelphia Zoo, Vastesaeger[29] at the Antwerp Zoo, Finlayson[8] at the London Zoo, and others,[6, 13, 20] they provide a panorama of the types of lesions which may occur in the animal kingdom. Studies of the former type may yield insights into the pathogenesis of arterial disease in a particular species, while studies of the latter type may permit the formulation of hypotheses concerning arterial disease in general.

In this article, we will present the results of a 5 year study of arterial disease in 405 mammals and birds from the Oklahoma City Zoo. On the basis of these findings, we will submit interpretations concerning the pathogenesis of arterial disease which differ somewhat from those currently in favor.

MATERIALS AND METHODS

In 1964 the University of Oklahoma Health Sciences Center opened the Institute for Comparative Pathology in conjunction with and on the grounds of the Oklahoma City Zoo. The purpose of the project was to study heart disease in zoo animals. Dr. Marshall E. Groover initiated the program and was the principal investigator until his departure in 1965. The material was gathered during a 5 year period from autopsies on

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animals dying in the Oklahoma City Zoo. A few specimens from the psychological research laboratory of Dr. W. B. Lemmon at the University of Oklahoma were also included, so that the grand total was 405 individuals and 162 species. Autopsies were consecutive for the most part, but all aortas were not suitable for study. Complete gross autopsies were done on all individuals, with histologic examination of most organs and tissues in approximately 50 per cent of the cases. Clinical records at the zoo were fairly good, but many animals died within a few weeks or months after acquisition, so that correlation of clinical and pathological data was not always possible.

Aortas and epicardial coronary arteries from large hearts were opened longitudinally, flattened on cardboard and fixed in 10 per cent formalin. After fixation, the vessels were stained with Sudan IV in isopropyl alcohol, using a modification[27] of the method originally described by Holman et al.[11] The extent of intimal involvement with fatty streaks, fibrous plaques, and/or complicated lesions was then graded independently by two observers and expressed as a percentage of the total intimal area. Representative blocks of arterial lesions were sectioned on a cryostat and stained with Oil Red - O - hematoxylin. The blocks were next embedded in paraffin and contiguous histologic sections were stained with hematoxylin and eosin and Weigert's elastic stain. Other stains were employed as indicated. Much of this work has been reported elsewhere.[2, 3, 21–25]

RESULTS

Aortic Lesions

Fatty Streaks. Fatty streaks were the most common lesions seen, being present in 61 (51 per cent) of 121 hoofed mammals, 60 (58 per cent) of 104 non-human primates, 7 (13 per cent) of 54 carnivores, none of 12 pinnipeds, 62 (86 per cent) of 72 birds, and 11 (26 per cent) of 42 exotic mammals; exotic mammals were those from the orders Insectivora, Edentata, Rodentia, Marsupialia, Hyracoidea and Tubulidentata. Fatty streaks were noted in all portions of the aortas, but tended to occur more frequently in the thoracic segments. Less than 5 per cent of the total surface of the aorta was involved in most of the individuals. Notable exceptions were a 3 year old male chimpanzee (Pan troglodytes) with 20 per cent, a squirrel monkey (Saimiri sciureus) with 40 per cent, a domestic turkey with 80 per cent, a common duck with 50 per cent, and two ostriches (Struthio camelus) with 60 and 65 per cent, respectively. On microscopic examination, these lesions consisted of focal deposits of Oil Red O positive material within a normal or slightly thickened intima. Intimal thickening, when present, was composed primarily of smooth muscle cells. The lipid droplets were usually small and evenly dispersed, although typical foam cells were seen occasionally, usually in birds or non-human primates. Some of the finely dispersed lipid droplets appeared to be extracellularly located, although this determination was not always easily made because of suboptimal preservation of tis-

sues. The lipid droplets tended to cluster along the intimal surface of the internal elastic membrane in the abdominal aortas, while in the thoracic aortas they often extended into the inner media.

Fibrous Plaques. Fibrous plaques were found in 57 (47 per cent) of 121 hoofed mammals, 19 (18 per cent) of 104 non-human primates, 19 (35 per cent) of 54 carnivores, 11 (92 per cent) of 12 pinnipeds, 42 (58 per cent) of 72 birds, and 8 (19 per cent) of 42 exotic mammals. Fibrous plaques were located primarily in the abdominal segments of the aortas, frequently at the iliac bifurcation or trifurcation. From traces to 3 per cent of the intimal surface of the aortas contained fibrous plaques in most of the individuals. Exceptions were an elderly male rhesus monkey (Macaca mulatta) with 15 per cent, 3 peacocks (Pavo cristatus) with 10, 12, and 15 per cent, respectively, a domestic turkey with 10 per cent, a Goliath heron (Ardea goliath) with 15 per cent, an argali (Ovis ammon) with 10 per cent, and 3 California sea lions (Zalophus californianus with 10, 10, and 11 per cent, respectively. Microscopically, the lesions were composed of smooth muscle and elastic tissue elements. In larger plaques, the smooth muscle cells of the intimal lesions were sometimes oriented in different planes. Most commonly, the cells nearest the media were oriented longitudinally or obliquely, while those adjacent to the lumen were oriented circumferentially. The internal elastic lamella was usually intact beneath small lesions and fragmented or absent beneath larger ones. Many fibrous plaques contained lipid droplets, which were usually distributed throughout the thickness of the lesions, but were most dense at the outer edges. These lipid droplets were often contained within smooth muscle cells. Foam cells and central accumulations of extracellular lipid were seen primarily in birds and non-human primates.

Atherosclerotic Plaques. Atherosclerotic plaques were found in 1 (1 per cent) of 121 hoofed mammals, 2 (2 per cent) of 104 non-human primates, none of 54 carnivores, none of 12 pinnipeds, 17 (24 per cent) of 72 birds, and 4 (10 per cent) of 42 exotic mammals. A plaque was called atherosclerotic when focal calcification, necrosis, accumulations of extracellular lipid and/or deposits of doubly refractive crystals were present in the central portion of the lesion. The percentage of the surface of the aortas involved by atherosclerotic plaques could not be readily estimated, since the diagnosis of atherosclerosis was usually made only after microscopic inspection. Atherosclerotic plaques were usually located in the abdominal segments of the aortas. The internal elastic lamella was often fragmented, but was sometimes intact, even beneath large atherosclerotic plaques. No ulcerated atheromatous plaques were noted, although one lesion in the abdominal aorta of an elderly male rhesus monkey (Macaca mulatta) contained a central crater-like depression, suggesting previous ulceration, and similar crater-like depressions were seen in plaques of several of the birds. One mural thrombus was found on microscopic examination loosely attached to a large fibrous plaque in the abdominal aorta of an adult female ostrich (Struthio camelus). This bird died following surgical correction of a prolapsed rectum, so that sepsis may have been responsible for the thrombus. This was the only mural thrombus found in the entire study.

Coronary Artery Lesions

The epicardial coronary arteries from 84 mammals and birds with large hearts were removed, stained with Sudan IV, and graded for arteriosclerotic involvement. Fatty streaks and/or fibrous plaques were found in 12 (32 per cent) of 38 hoofed mammals, 5 (29 per cent) of 17 non-human primates, 2 (20 per cent) of 10 carnivores, none of 8 pinnipeds, 4 (57 per cent) of 7 birds, and 3 (60 per cent) of 5 exotic mammals. The majority of these lesions were small, involving 5 per cent or less of the intimal surface. In one white-tailed deer (Odocoileus virginianus) and one sitatunga (Tragelaphus spekei), fibrous plaques covered 10 and 15 per cent of the intimal surface, respectively. None of the lesions produced significant stenosis and no large myocardial scars or infarcts were found.

Microscopically, the fatty streaks consisted of slight intimal thickenings which contained Oil Red O positive droplets. The lipid was usually located within smooth muscle cells. In several non-human primates, birds, and exotic mammals, typical foam cells were seen. The fibrous plaques were composed of longitudinally oriented smooth muscle cells and elastic fibers, and frequently contained lipid droplets. In one Nubian ibex (Capra ibex), the lipid droplets were extremely numerous, yet no foam cells were present. Although none of the lesions were classified as atherosclerotic, fibrous plaques in two animals, one white-tailed deer (Odocoileus virginianus) and one stork (Jabiru mycteria), contained central, hypocellular, lipid-rich zones which suggested early atheromatous "transformation."

The coronary arteries in medium-sized and small hearts were examined in 54 non-human primates using a modification of the method of Clarkson.[4] In medium-sized hearts, blocks were removed from the main left coronary artery, the proximal portions of the left anterior descending and circumflex branches of the left coronary artery, and the proximal portion of the right coronary artery. Three frozen step sections from half of each block were stained with Oil Red O, and the remainder of the block was embedded in paraffin for a single hematoxylin and eosin section. In the small hearts, one or two coronal blocks including both ventricles were removed and processed in the same manner. All of the arteries greater than 30 microns in diameter were then counted, and the total was divided into the number of arteries with intimal disease to derive a score for each heart. Lesions consisting of minor intimal thickenings which contained Oil Red O positive material were found in 10 (19 per cent) of the 54 hearts. One to 6.5 per cent of the arteries were involved in the majority of the hearts with lesions. In one male bush baby (Galago senegalensis), 11 per cent of the small arteries had lesions. Significant luminal stenosis was not found in any of the hearts.[22]

The coronary arteries in medium-sized and small hearts were not systematically examined in the other species of mammals and birds.

Cerebral Artery Lesions

The arteries of the circle of Willis were examined systematically in the brains of 80 non-human primates. In the large brains, the circle was removed and the vessels opened longitudinally. In the great majority of

brains which were too small to be examined by this method, the arteries were inspected unopened using a dissecting microscope or a hand lens. It is possible that very small intimal thickenings were overlooked by the latter method. However, it is doubtful that any lesion of significant size escaped detection, since most of these arteries were virtually transparent. Lesions were found in 2 of the 80 animals, a 3 year old male and a 9 year old female chimpanzee (Pan troglodytes). Lipid-rich plaques were present at the origin of the basilar and intracranial internal carotid arteries. These plaques contained many foam cells and occupied up to 50 per cent of the luminal diameter. A hypocellular, lipid-rich area with focal calcification characteristic of atherosclerosis was seen in the center of a lesion in the intracranial internal carotid artery of the older animal. There was no evidence of infarction of the brain in either animal.

The cerebral arteries were not systematically studied in the brains of the other species of mammals and birds.

DISCUSSION

The findings in the aortas of the various species of captive mammals and birds are interesting for several reasons. As more and more surveys of this type are reported, it becomes clear that fatty streaks, fibrous plaques and atherosclerotic plaques occur in a large number of diverse species. In our material, and also that of Vastesaeger[29] and Finlayson,[8] true atherosclerotic plaques with areas of central necrosis and lipid and/or cholesterol accumulations were seen much more commonly in birds than in any of the other mammals or reptiles. This may be due to the fact that birds have higher blood pressures[28] than mammals, and also higher serum cholesterol levels,[8, 29] although admittedly, information on both of these parameters is limited. It does seem certain that being a bird is more important than the type of diet consumed, since fish-eating birds have far more atherosclerosis than fish-eating mammals, carnivorous birds have far more atherosclerosis than carnivorous mammals, graminiverous birds have far more atherosclerosis than graminiverous mammals, and so on.

It is difficult to correlate atherosclerosis with diet in a relatively small group of zoo animals, because of the large number of variables which affect these populations. Precise ages of individuals are frequently unknown, the duration of time in captivity differs, the composition of prepared rations is not rigorously controlled, and the diets of some of the animals are supplemented by morsels from the public. In addition, little is known of the heredity of individual animals, diagnosis of intercurrent disease often must depend entirely upon the analysis of post mortem findings, and the degree of success of animals' adaptation to captivity frequently cannot be measured. We have attempted to correlate the prevalence of atherosclerosis with the diet, time in captivity, age, and cause of death in the present group of 72 birds. Although these data could not be statistically analyzed, there appeared to be no obvious correlation between the variables cited and the prevalence of atherosclerosis. This was also true when the habitual diet in the birds was correlated with the prevalence of atherosclerosis; that is, the fish-eating birds appeared to

have as much atherosclerosis as the meat-eating birds, the graminiverous birds, and the insect-eating birds.

After a similar analysis of a larger sample of mammals and birds from the London Zoo, Fiennes[7] thought that those individuals consuming an unnatural diet had more atherosclerosis than others. Unnatural diets were primarily graminiverous diets which, by virtue of captivity or recent evolution, had replaced some other type of diet. Others who have studied arterial disease in populations of captive and free-ranging animals have been unable to indict any particular foodstuff for the production of atherosclerosis.

The occurrence of atherosclerotic lesions in the epicardial coronary and the basilar and intracranial internal carotid arteries of 2 chimpanzees is important because these lesions were more advanced than those which were present in the aortas of these 2 animals. These 2 chimpanzees were 3 and 9 years of age, respectively, which is roughly comparable to 6 and 18 years of age in man. They had spent most of their lives in captivity, consuming a diet containing up to 10 per cent of total calories as fat. This is probably more fat than the average chimpanzee consumes in nature, but does not approach the levels (usually a minimum of 35 per cent of calories as fat with added cholesterol) which have been fed to non-human primates in experiments on atherogenesis. The predominant coronary and cerebral atherosclerosis in these 2 chimpanzees parallels that which is often found in young Western males dying from myocardial infarction in the third and fourth decades of life. Similar findings were reported by Vastesaeger,[30] who found coronary atherosclerosis in 2 chimpanzees from the Antwerp Zoo. The lesion in one of the animals was complicated by occlusive thrombosis. Relatively extensive cerebral artery atherosclerosis has been noted in other chimpanzees.[1]

The point to be made is that several captive chimpanzees have acquired predominant coronary and cerebral artery atherosclerosis without being exposed to a high fat diet or excessive cigarette smoking. Unfortunately, other data such as blood pressure measurements were not available in most of the animals. A single post mortem serum cholesterol concentration obtained on our older animal was not particularly high (192 mg. per 100 ml.). The reason for this predominance of atherosclerosis in the coronary and cerebral arteries in captive chimpanzees is not known, and there are not enough data available to be certain that these changes do not occur in the wilds. Only one attempt has been made to induce atherosclerosis in chimpanzees through high fat, high cholesterol feeding. In this study, it is interesting that although there were more aortic fatty streaks in the experimental animals than in the controls, this difference was less pronounced in epicardial coronary arteries, and there was no difference in the cerebral arteries.[1]

The above information, while incomplete, suggests that in the chimpanzee, factors other than those currently under suspicion (diet, cigarette smoking, etc.) may be involved in the production of precocious coronary and cerebral artery atherosclerosis. Both of our animals had adjusted poorly to captivity, showing neurotic traits such as stereotyped posturing, hoarding of food and other objects, and poor socialization with peer animals in the colony. Whether or not these factors have anything to do

with precocious coronary and cerebral artery atherosclerosis remains to be seen.

The majority of lesions found in the present study were fatty streaks and fibrous plaques. These lesions closely resembled those which are common in man during the first four decades of life, although in general, the lesions in animals contained less lipid. Because the arteries of most mammals and birds are morphologically similar to those of man, it is reasonable to assume that fatty streaks and fibrous plaques could arise through similar pathogenic mechanisms in animals and man. Examination of our material yields evidence that the proliferation of smooth muscle cells in the intima may occur without the presence of lipid within these cells. For example, fibrous plaques were found in 11 of 12 pinnipeds (seals and sea lions), most of whom were adolescents or young adults. These lesions were located primarily in the abdominal aortas and distal to intercostal branch orifices in the thoracic aortas. The largest plaques were as thick as the underlying media. The plaques were composed of smooth muscle cells and elastic tissue and were morphologically identical to the early fibrous plaques of man, with one exception – they contained no stainable lipid. Moreover, no fatty streaks were present in the younger seals and sea lions with fewer fibrous plaques. Therefore, we must conclude that the insudation of lipids into the intima had nothing to do with the formation of the fibrous plaques in the seals and sea lions. Lindsay and Chaikoff[13] reached a similar conclusion concerning the role of lipids after their extensive study of naturally occurring arteriosclerosis in animals.

This is contrary to current opinion concerning the pathogenesis of the early proliferative lesion in human atherosclerosis; smooth muscle cells are thought to proliferate in response to the accumulation within their cytoplasm of excess lipids from the plasma.[10] One might argue that seals and sea lions are different than man and, therefore, what is true for one is not necessarily true for the other. However, we must not forget that the lipid insudation–intimal smooth muscle cell proliferation theory was derived primarily from experiments using cholesterol-fed rabbits and other animals. It would be difficult to decide which was more different than man, the sea lion or the rabbit. The decision is not so difficult, however, when the sea lion is compared with the cholesterol-fed rabbit.

The hoofed mammals (Orders Artiodactyla and Perissodactyla) were another group in which lipids appeared to play very little part in the pathogenesis of the elevated arterial lesions observed. Fatty streaks were seen in 61 of 121 hoofed mammals, especially young ones, and were located primarily in the thoracic segments of the aortas. Fibrous plaques were seen in 57 of 121 hoofed mammals, primarily adults, but were located almost exclusively in the abdominal segments of the aortas. Therefore, it would appear that in hoofed mammals, fatty streaks did not evolve into fibrous plaques.

There is also evidence in humans which indicates that fatty streaks may not be converted into fibrous plaques. Holman[12] compared aortas in blacks and whites from 0 to 40 years of age from New Orleans and found even though the blacks had more fatty streaks, the whites had more fibrous plaques. Fatty streaks occupied approximately 25 per cent of the

surface area of the aortas in blacks from age 10 onward. In whites, fatty streaks gradually increased until approximately 22 per cent of the aorta was involved at 35 years of age. Significant numbers of fibrous plaques began to appear in both races at 25 years of age, gradually increasing to involve around 8 per cent of the aorta in blacks, and 15 per cent of the aorta in whites at 40 years of age. More extensive studies by these investigators in 19 different race-population groups revealed that the extent of fatty streaks in the aorta at 15 to 39 years of age did not predict the extent of raised lesions in the aorta at 45 to 54 years of age in any of the groups.[14] The extent of coronary artery fatty streaks at 15 to 39 years of age did predict the extent of coronary artery raised lesions at 45 to 54 years of age in the 14 non-black race-population groups, but not in the 5 black groups. The authors felt that, in general, fatty streaks were converted into fibrous plaques, but that in blacks, some factor delayed the conversion.

It is also possible that factors other than lipid insudation may cause intimal proliferation and elevated lesions. It is important to determine what these other factors are, for after all, it is the elevated lesion which causes ischemic difficulties in man. The fatty streak is significant only if it leads to the formation of an elevated lesion; by itself, it is innocuous. We have just completed experiments showing that chronic intermittent low intensity electric shock is associated with increased numbers of aortic fibrous plaques in miniature pigs.[26] The shock was delivered through the floor at hourly intervals for 6 months. The shock was not strong enough to produce severe pain, but the experimental group soon appeared more watchful and wary than the controls. The control pigs had more aortic fatty streaks than the shocked pigs, which suggests that lipids were not involved in whatever mechanism caused the increased intimal smooth muscle cell proliferation in the latter.

At the present time, it would appear that considerable uncertainty exists as to whether or not fatty streaks are the precursors of elevated fibrous plaques. In view of this uncertainty, it would probably be wise to postpone the large scale restriction of saturated lipids and cholesterol in the diets of children, at least until there is stronger evidence indicating that such restriction will reduce the extent of elevated lesions in adulthood.

Another important question in human atherosclerosis involves the pathogenesis of central plaque necrosis. Many investigators feel that this necrosis is due to the accumulation of lipids within the cells of the plaque, said accumulation causing cell death and rupture with release of lipid into the extracellular space. It is also possible that cell injury is produced by some other mechanism, and that lipids then accumulate within the cells because they are injured. It is well known from observation of other types of pathologic processes, that lipids accumulate within cells which are injured, such as in steatonecrosis of the liver in chronic alcoholism, and fatty degeneration of the myocardium in anemia. The material in the present study was not ideally suited to answer this question, since typical atherosclerotic lesions were relatively uncommon. It should be noted, however, that in the atherosclerotic plaques in giant anteaters (Myrmecophaga tridactyla) and aardvarks (Orycteropus axer), central necrosis appeared to precede lipid accumulation. Moreover,

frequent small areas of focal necrosis, apparently involving smooth muscle cells, were found within fibrous plaques in a number of species. These areas were usually seen in the musculoelastic plaques which did not contain excessive lipid and which were not extremely thick, so that hypoxia did not appear to be responsible for the necrosis. The areas of necrosis were not accompanied by a significant acute or chronic inflammatory response, but were characterized by loss of nuclei and accumulation of small calcium and sometimes lipid granules within the cytoplasm, suggesting a degenerative process of some kind. It is interesting that these areas were also present in the fibrous plaques of several of the miniature pigs receiving chronic electric shock.

When the arteries of mammals and birds are compared with those of man, the most striking difference which emerges is the lack of mural thrombi in the former. Even the animal aortas with multiple saccular aneurysms contained no mural thrombi. This is in marked contrast to the human situation, in which an aneurysm without a mural thrombus is a rarity. The paucity of mural thrombi in mammals and birds is not entirely due to the lack of arterial lesions. The aortas of several birds in the present study had 60 to 80 per cent of their surfaces covered by lipid-containing lesions and the lumens of occasional branch arteries were 75 per cent occluded by atherosclerosis; yet the only mural thrombus was found by accident on microscopic examination. This truly remarkable difference between animals and man probably explains why animals have so few ischemic complications, even in the face of occasional extensive atherosclerosis, and conversely, why man has so many ischemic complications, sometimes in the face of only moderate atherosclerosis.

In view of the above, one might anticipate that the control of mural thrombosis in man would be the best way to effect an immediate reduction in the incidence of the ischemic complications of atherosclerosis. This does not mean that efforts to control the early proliferative aspects of atherosclerosis should be abandoned.

SUMMARY

We have described the results of a survey of arterial disease in 405 mammals and birds representing 162 species from the Oklahoma City Zoo. Typical atherosclerotic plaques were common in the birds, being found in the aortas of 24 per cent of 72 individuals. The prevalence of aortic atherosclerosis in birds could not be correlated with the type of diet consumed in captivity or in nature. Fish-eating birds had as much atherosclerosis as meat-eating birds, grain-eating birds, and insect-eating birds.

Predominant epicardial coronary and intracranial cerebral artery atherosclerosis was found in 2 chimpanzees, and similar findings have been reported by others in captive chimpanzees. These lesions were analogous to those which occur in young Western males dying with myocardial infarction. The spontaneous lesions in the chimpanzees were not associated with a high fat diet but were possibly associated with neurotic behavior. Predominant coronary and cerebral atherosclerosis was not

produced by the one high fat, high cholesterol feeding experiment which has been conducted in chimpanzees.

Fatty streaks and fibrous plaques were quite common in many species of mammals and birds. In seals and sea lions, aortic fibrous plaques were plentiful, and were similar in morphology and distribution to those which occur in humans. However, the fibrous plaques in seals and sea lions contained no stainable lipid, indicating that some mechanism other than lipid insudation was responsible for the proliferation of intimal smooth muscle cells. The hoofed mammals were another group in which lipids appeared to play little part in the pathogenesis of elevated fibrous plaques. Fatty streaks were common in young hoofed mammals, but were localized to the thoracic aortas. Fibrous plaques were common in older hoofed mammals, but were localized to the abdominal aortas. Moreover, studies of 19 race-population groups of humans in The International Atherosclerosis Project indicate that the extent of aortic fatty streaks at 15 to 39 years of age does not predict the extent of aortic fibrous plaques at 45 to 54 years of age. The cumulative evidence seems to show that factors other than lipid insudation may be important in the production of elevated fibrous plaques. Experiments recently completed in our laboratory indicate that chronic low intensity electric shock is associated with increased proliferation of aortic fibrous plaques in miniature pigs.

An important question in human atherosclerosis involves the pathogenesis of central plaque necrosis. Many investigators feel that this necrosis is due to the accumulation of lipids within the cells of the plaque, said accumulation causing cell death and rupture with release of lipids into the extracellular space. It is interesting that in the atherosclerotic plaques of giant anteaters and aardvarks, central plaque necrosis appeared to precede lipid accumulation. Moreover, frequent areas of focal plaque necrosis, apparently involving smooth muscle cells, were found within fibrous plaques in a number of species. These areas of focal necrosis were also present within fibrous plaques of some of our experimental pigs receiving chronic electric shock.

Virtually no mural thrombi were seen in the study of zoo mammals and birds, even though the aortas of several of the birds had 60 to 80 per cent of their surfaces covered by lipid-containing lesions. This is in marked contrast to the human situation, in which mural thrombi are extremely common. This remarkable lack of mural thrombi probably explains why ischemic complications are seldom seen in animals, despite occasional examples of extensive atherosclerosis, and conversely, why ischemic complications are so common in man, sometimes in the presence of only moderate atherosclerosis. Because of this, one might anticipate that the control of mural thrombosis in man would be the best way to effect an immediate reduction in the incidence of the ischemic complications of atherosclerosis in man.

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Atherosclerosis

Its Hemodynamic Basis and Implications

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Application of the laws of fluid mechanics to the natural conditions in the circulatory system reveals a rational and demonstrable basis for the localization, inception, and progressive development of atherosclerosis. Atherosclerosis does not occur at random locations. It does occur uniformly at specific sites of predilection which can be precisely defined, predicted, and produced by applying the principles of fluid mechanics. The areas of predilection for atherosclerosis are consistently found to be the segmental zones of diminished lateral pressure produced by the forces generated by the flowing blood. Such segmental zones of diminished lateral pressure are characterized by curvature, branching, bifurcation, tapering, or external attachment (Figs. 1 through 5). Although these anatomic configurations occur in many variations of geometry, their common feature is a pattern of blood flow conducive to the production of localized areas of diminished lateral pressure. This is the initial stimulus. Atherosclerosis may therefore be considered the reactive biologic response of blood vessels to the effect of the laws of fluid mechanics, namely, the forces (diminished lateral pressure) generated by the flowing blood at sites of predilection determined by local hydraulic specifications in the circulatory system.

Previous reports from this laboratory beginning in 1957 have described the prerequisite hydraulic conditions and the basic laws of fluid mechanics which are relevant to the development of atherosclerosis in the circulatory system.[6, 8] The hemodynamic mechanism for the localization, inception, and progressive pathologic changes that characterize atherosclerotic lesions have also been described.[11] Similarly, characteristics of blood flow in arteries, flow patterns, and certain theoretical calculations have been identified.[1, 4, 7, 10] In addition, hemodynamically in-

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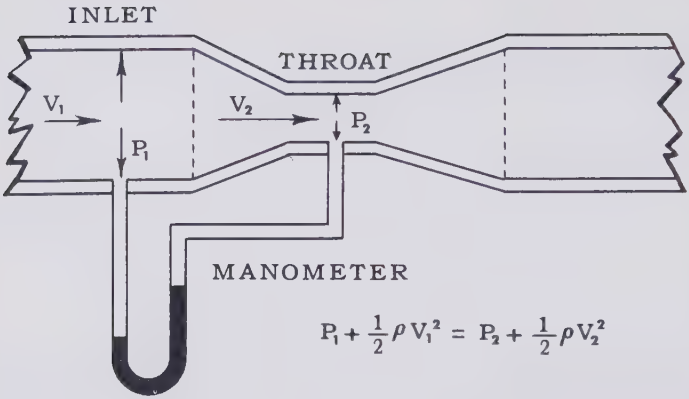

Figure 1. *Venturi meter and Bernoulli's equation.* Flow in a tube with converging boundaries causes the lateral pressure to be reduced at the narrow portion where the velocity is increased. Bernoulli's theorem states that the sum of the pressure and the square of the velocity times $\rho/2$ is constant if fluid flows from point 1 to point 2 on the same streamline. (*From* Texon, M.: Arch. Intern. Med., *99*:418–427, 1957, with permission.)

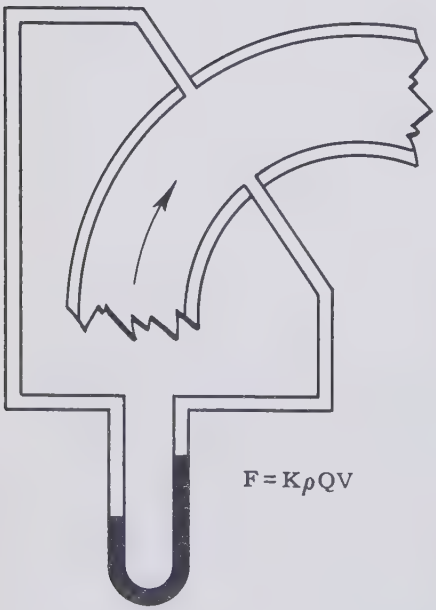

Figure 2. *Elbow flow meter and force equation.* In curvilinear motion, the lateral pressure is increased along the outer wall and decreased along the inner wall, owing to the effective centrifugal force. (*From* Texon, M.: Arch. Intern. Med., *99*: 418–427, 1957, with permission.)

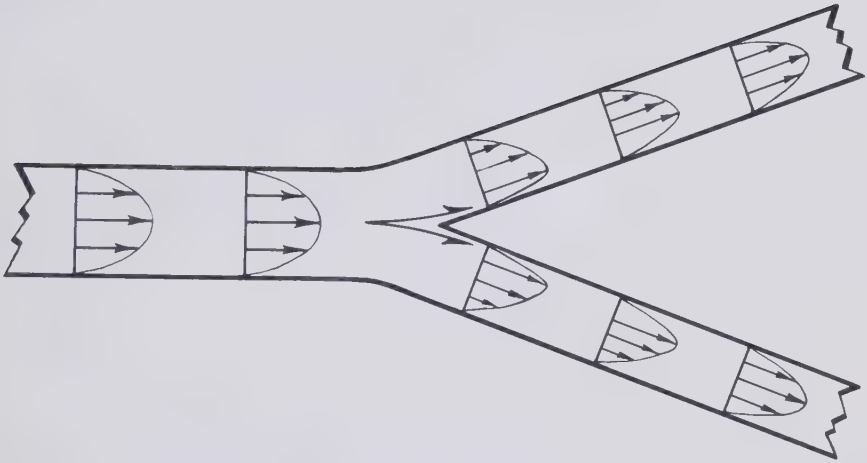

Figure 3. *Velocity distribution for streamline flow along a tube and bifurcation.* The velocity of flow at a cross section of a tube increases from the wall toward the center. Division of the axial stream results in a relative increase in velocity and a decrease in lateral pressure at the medial walls, owing to the local curvatures required of the streamlines. (*From* Texon, M.: Arch. Intern. Med., *99*:418–427, 1957, with permission.)

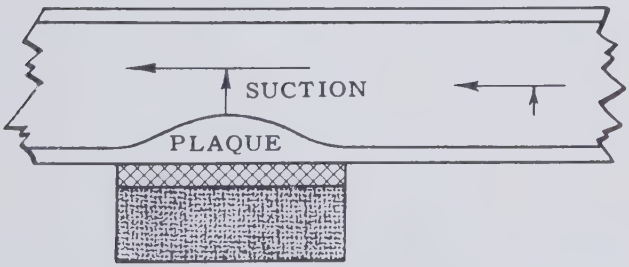

Figure 4. *Effect of diminished lateral pressure at zone of external attachment.* The fixation resists the tendency of the flowing blood to move the wall of the vessel inward toward the axial stream. (*From* Texon, M.: Arch. Intern. Med., *99*:418–427, 1957, with permission.)

duced atherosclerotic lesions in dogs have been produced by the surgical alteration of vascular configurations under controlled conditions.[2, 3, 12] The naturally and experimentally produced lesions in dogs and the naturally occurring lesions in humans have been illustrated and analyzed both pathologically and mathematically.[9] The atherosclerotic changes are demonstrated to be due consistently to the same specific stimulus – the diminished lateral pressure – as determined and produced by the characteristics of flowing blood and the local hydraulic specifications.

Variations as well as similarities in the severity of atherosclerosis in different individuals and in different locations in the circulatory system of the same individual are principally due to differences as well as similarities in local hydraulic specifications. The velocity and pattern of blood flow, the caliber of the lumen, and the anatomic pattern are of importance. A biologic factor must also be considered, namely, the local reparative reaction or pathophysiologic response of the intima to the diminished lateral pressure generated by the flowing blood. It is here that the nature and degree of atherosclerotic change may be modified or influenced by differences in tissue structure and differences in tissue response arising from genetic and species characteristics.

The roles of associated or contributory factors such as age, sex, race, heredity, diet, nutritional status, habitus, lipid metabolism, cholesterol, obesity, drugs, trace elements, associated diseases, enzyme systems, hormones, hypertension, occupation, and emotional stress require re-evaluation as secondary or modifying factors. Not one of these factors is always present; nor is any particular combination present as a common denominator (sine qua non) or as a primary factor responsible in a causative sense for atherosclerosis. None of these factors can create or cause atherosclerosis. Atherosclerosis is found in both men and women, in the relatively young and in the elderly, in hypertensive as well as in normotensive persons, and in lean as well as in obese individuals. Notwithstanding available studies of the statistical association of atherosclerosis with lipids, diet, sex, race, occupation, hypertension, smoking, and emotional stress, proof of the causal relation of these factors to atherosclerosis is not thereby proved or demonstrated. A statistical association per se does not constitute scientific proof of a causative mechanism. A primary causative factor or mechanism for atherosclerosis must be a common denominator operating in all cases so that it determines the presence as well as the absence of atherosclerosis in all cases and in any given case.

The localized decrease in static pressure at zones of predilection produces, in effect, a local suction action upon the intima at some phase of pulsatile flow in the cardiac cycle. The intima is subjected to the lifting or pulling effect of the flowing blood upon the endothelium and subjacent cells. This is the initial stimulus. The response is the local biologic change, a reparative or reactive thickening, resulting from the proliferation of endothelial cells and fibroblasts.

With continuing blood flow, progressive changes occur in situ. These may include elastic tissue changes, cellular infiltration, collagen deposition, lipid changes, calcification, and vascularization. The pathologic processes inherent in atherosclerosis may be stationary for long periods

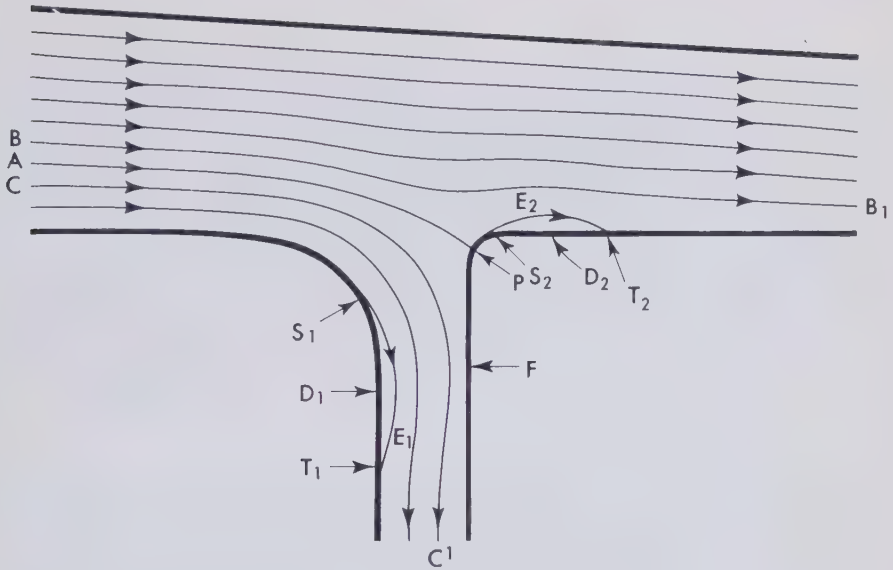

Figure 5. *Ostial or branch lesion.* Flow pattern at site of branching in a two-dimensional flow showing zones of low pressure and sites of atherosclerotic changes. Precise localization of the atherosclerotic plaque is determined by local hydraulic specifications which include velocity of flow, angle of branching, ratio of diameter of main stem to diameter of branch, and shape of ostial orifice. (*From* Texon, M.: Bull. N.Y. Acad. Med., *48*:733–740, 1972, with permission.)

of time or slowly progressive. Relatively quick or sudden changes may also occur. Ulceration of an atherosclerotic plaque may result from lifting off or shearing off of the superficial layers. Blood elements may form a thrombus at the raw or ulcerated surface. The thrombus may enlarge to a partially occlusive or totally occlusive degree by the accretion of additional blood elements. The progressive pathologic process, by encroaching on the lumen, produces occlusive changes of all degrees which are the result of the biologic or cellular response to the continuing mechanical stresses at segmental zones of the intima, determined by the flowing blood and local hydraulic specifications.

In summary, all the data from human specimens, model hydraulic systems, the laws of fluid mechanics, and the experimental production of hemodynamically induced arterial lesions in dogs support the hemodynamic basis of atherosclerosis and compel the conclusion that the effect of the laws of fluid mechanics—vascular dynamics—is the primary causative factor in the localization, inception, and progressive development of atherosclerosis.

FINDINGS AND IMPLICATIONS OF THE HEMODYNAMIC BASIS OF ATHEROSCLEROSIS

Flowing blood, by virtue of its motion, possesses kinetic energy, and produces mechanical stresses upon the walls of the blood vessels. The

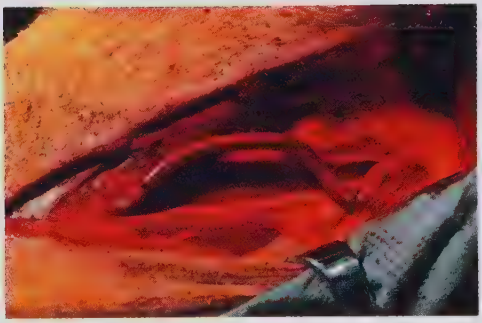

Fig. 6A

Fig. 7A

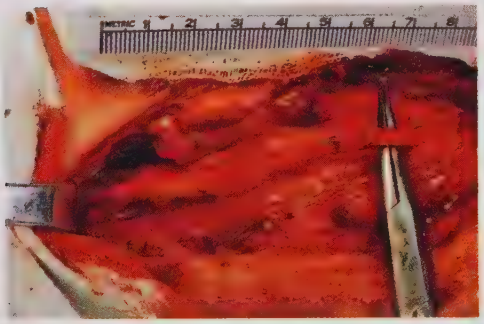

Fig. 6B

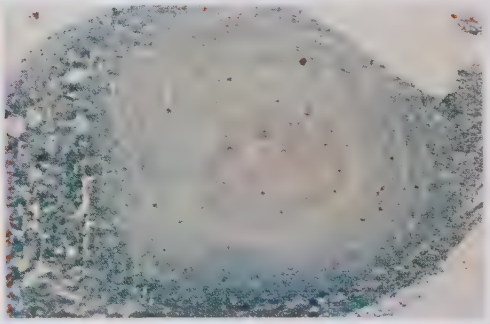

Fig. 7B

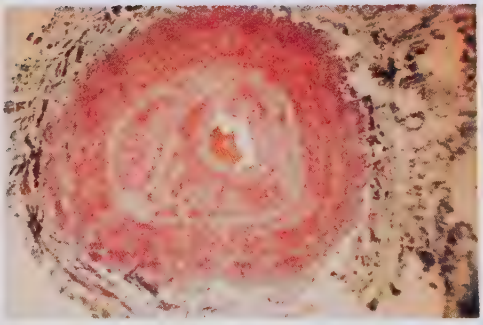

Fig. 6C

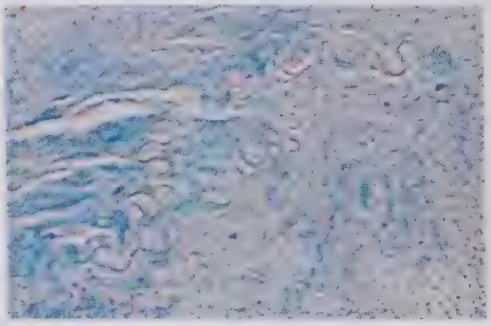

Fig. 7C

Figure 6. *A, Surgical preparation.* Curvature produced by interposing a segment of carotid artery between ends of transected femoral artery (Dog No. 5278). *B,* Same preparation 3 months later. Normal diet. Curvatures have straightened. Vessel has contracted both circumferentially and longitudinally. *C,* Microscopic cross-section reveals reduction in lumen by intimal and fibroblastic proliferation.

Figure 7. *Ductus arteriosus in a 59 year old woman. A,* Gross specimen. *B,* Microscopic cross-section reveals obliteration of lumen by fibroblastic proliferation. *C,* Remnants of internal elastic layer.

Fig. 8*A*

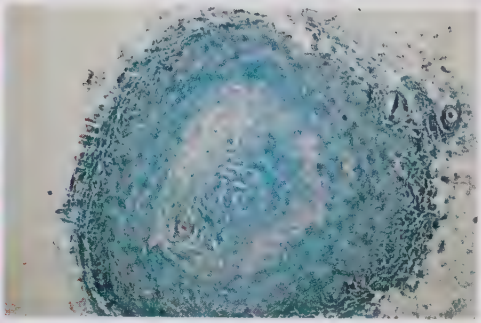

Fig. 8*D*

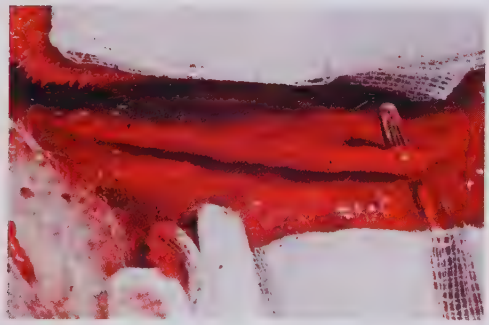

Fig. 8*B*

Fig. 8*E*

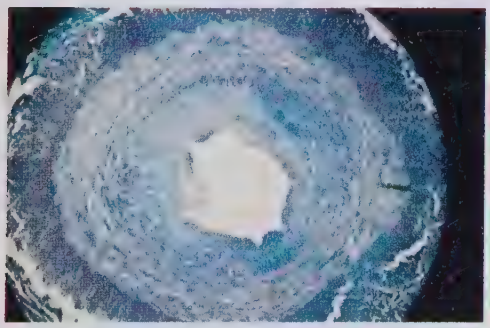

Fig. 8*C*

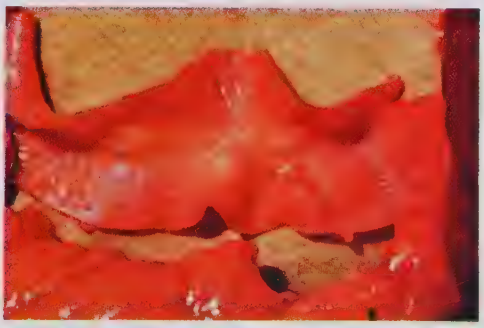

Fig. 9

Figure 8. *A*, *Surgical preparation.* Carotid to femoral isometric autograft (Dog No. 2512). Immediately after operation. *B*, Carotid to femoral isometric autograft (Dog No. 2512) 14 months after operation. Normal diet. *C*, Carotid artery showing reduction of lumen by intimal and fibroblastic proliferation 14 months after operation. Normal diet. *D*, Carotid artery at a section distal to *C* showing obliteration of lumen by fibroblastic proliferation. Vessel is transformed into a fibrous cord. *E*, Microscopic section reveals remnants of internal elastic layer.

Figure 9. *Human splenic artery, woman aged* 55. Note relatively uniform diameter and three curves having similar radii of curvature with similar lesions on the convex side of each curvature. (*From* Sandler, M., and Bourne, G. H., eds.: Atherosclerosis and Its Origin. New York, Academic Press, 1963, pp. 167–195, with permission.)

normal stresses, perpendicular to the walls (σ), and the shear stresses, parallel to the walls (τ), are due chiefly to the anatomical pattern or geometry and the velocity distribution in the blood vessel.[9] These fluid stresses and patterns of blood flow have been computed to some extent for particular cases by digital computations.[5]

A theoretically optimal condition of any blood flow would be one that meets the physiologic blood requirement of the organ supplied while exerting a minimal mechanical stress (diminished lateral pressure or tensile stress) upon the intima or wall of the blood vessel.

Normal Range of Blood Velocity

In a vessel of fixed diameter the volumetric blood flow is directly proportional to the velocity of blood flow; ($Q = AV$). A velocity of flow above the ideal physiologic limit is conducive to the production of segmental zones of diminished lateral pressure with resultant intimal proliferation and further atherosclerotic changes at the sites of predilection. Conversely, a velocity of blood flow and lateral pressure below a critical level may fail to maintain adequate mechanical patency of the lumen because of elasticity or external pressure, and intimal proliferation may then encroach upon the lumen (Figures 6, 7, 8). In some instances external pressure or twisting of a blood vessel partially occludes the lumen and diminishes the blood flow to such a degree that intimal proliferation may further encroach upon the lumen and even transform the vessel into a fibrotic cord (Figs. 6 to 8).

Consider a blood vessel with a normal pressure and velocity of blood flow. The diameter will vary between normal limits depending on the systolic and diastolic pressure in the vessel. If, at a given site, the blood flow is permanently altered by disease, external pressure or by surgical intervention so that the systolic and diastolic pressures are reduced, both the diameter and length of the vessel distally will be correspondingly reduced by the contraction of the elastic tissue in the wall. If the blood flow is still further reduced so that, despite a maximum reduction in diameter and length resulting from contraction of elastic tissue fibers, patency of the lumen cannot be maintained by the blood pressure, the lumen collapses or becomes gradually obliterated by endothelial and fibroblastic proliferation. This process should not be considered a form of atherosclerosis but rather a reparative biologic or cellular response which serves to occlude an unused lumen and to transform the vessel into a fibrous cord (Figs. 6 to 8). This appears to be a mechanism for the occlusion of bypass grafts, namely, intimal and fibroblastic proliferation secondary to diminished blood flow. It is of particular interest and importance to vascular surgeons.

It is apparent that a normal physiologic range of blood volume requires a normal range of pressure and velocity of blood flow which minimizes intimal proliferation due to either excessively high blood velocity or excessively low blood velocity.

Similar Hydraulic Conditions

Similar hydraulic specifications and similar vascular configurations produce similar atherosclerotic lesions as illustrated by the tortuosity of a human splenic artery (Fig. 9). This specimen presents three curves and a

relatively uniform diameter without branching vessels. Similar segmental atherosclerotic plaques are found on the convex surface of each of the three curvatures.

Blood Flow—A Life Requirement

Atherosclerosis, beginning with intimal proliferation, is an ongoing process which appears in utero as soon as blood begins to flow in definitive channels. The continuous operation of local hydraulic forces throughout life makes further pathologic changes inherently possible. Atherosclerosis is a price we pay for blood flow as a requirement of life. Atherosclerotic lesions are consistently found at sites of predilection at all ages. The severity of the process does not bear a linear relation to age but rather to time in relation to local hydraulic specifications (Fig. 10).

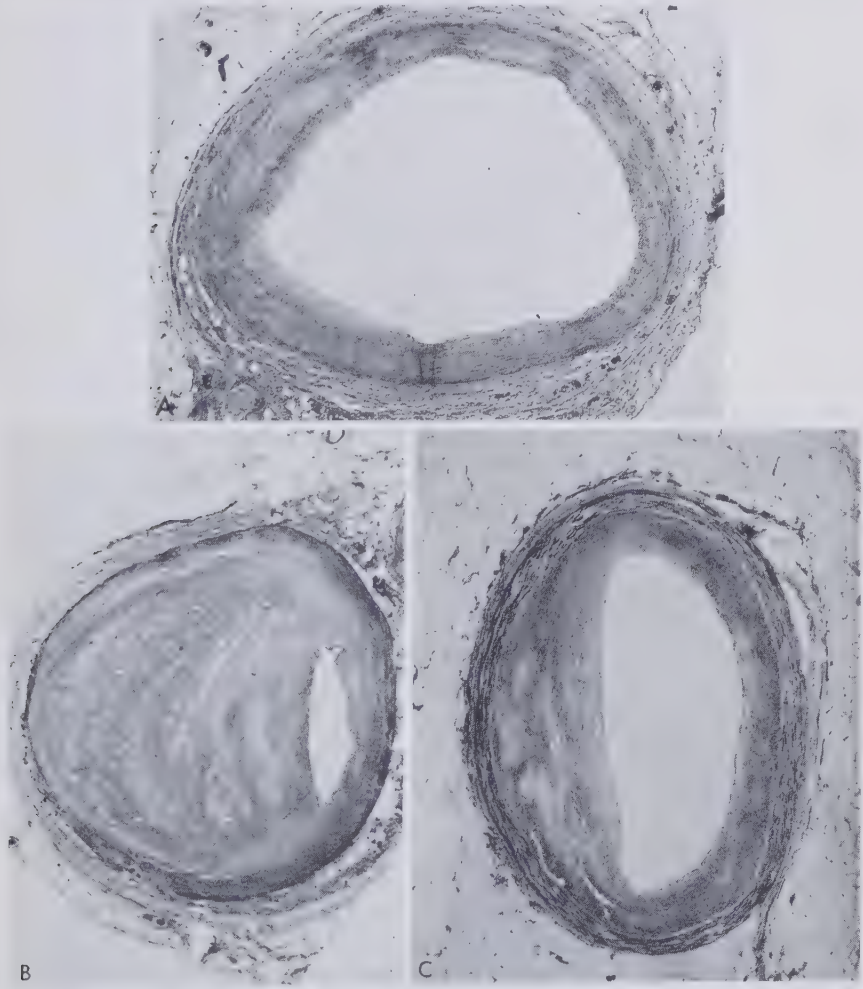

Figure 10. *Coronary arteries. A*, Coronary artery (L. A. D.), Negro man, aged 24. *B*, Coronary artery (L. A. D.), white woman, aged 29. *C*, Coronary artery (L. A. D.), white man, aged 56. Note that reduction in lumen by atherosclerotic disease does not bear a linear relation to chronologic age (see text). (*From* Sandler, M., and Bourne, G. H., eds.: Atherosclerosis and its Origin. New York, Academic Press, 1963, with permission.)

The fact is that atherosclerosis, as a progressive arterial disease, or its pathologic complications, are a major cause of human illness, disability and death.

Stimulus Versus Response

While the development of atherosclerosis must depend upon the operation of its primary etiologic factor (local diminution in lateral pressure produced at sites of predilection by the effects of flowing blood) the rate of development and severity of the disease may be modified by biologic factors. It is here that genetic tissue differences in reactive or reparative response to injury at the cellular level may determine the nature and degree of atherosclerotic change in each individual.

Cure Versus Control or Modification

Atherosclerosis is a progressive pathologic process or disease. Apart from localized "reaming" procedures, bypass operations, and the replacement of surgically accessible diseased vessels, atherosclerosis, as a disease which affects all individuals in varying degrees, cannot be cured in the sense of curing or eliminating an infectious disease. Blood flow is necessary for life and blood flow inherently causes atherosclerotic changes in blood vessels. The best we can hope to achieve is to minimize or retard the development of atherosclerosis by controlling the relevant hydraulic specifications which control the development of atherosclerosis. It may be noted that not all the hydraulic factors which contribute to the development of atherosclerosis are of equal importance, nor are they all amenable to change, manipulation or control. Thus the anatomic pattern, such as angles of branching, radii or curvature, attachments, and calibers of lumens, are largely determined by heredity and development. Similarly, the biologic response of the intima to the stimulus of the hydraulic forces is probably determined by heredity as a racial or species characteristic.

A promising area of specific research lies in the study of the velocity of blood flow. An increase in blood velocity, if other factors remain unchanged, must produce more severe atherosclerosis. A decrease in blood velocity, if achieved without impairing the metabolic requirements or vital centers or organs, may be expected to minimize or retard the development of atherosclerosis and its progressive pathologic complications. A pharmacologic agent or a physiologic method may be found or developed to achieve this goal.

Another valid research approach to the control of atherosclerosis lies in a study of methods to alter or modify the biologic factor, namely, the reactive reparative response of the intima or walls of blood vessels to the forces generated by the flowing blood.

Characteristics of Blood Flow in Arteries Which Influence the Development of Atherosclerosis

In contrast to steady flow, which characteristically produces either a relatively constant compressional or tensile stress at a given site in a blood vessel, pulsatile flow may be characterized by alternating compressional and tensile stresses. In a pulsatile flow, a high mean velocity, a

high peak velocity, and a high rate of change of velocity may be more prone to promote the development of intimal proliferation and atherosclerotic change than a lower average rate of flow, a lower peak velocity, and a lower rate of change of velocity. In this sense, a pulsatile flow which can be made to approach the characteristics of steady flow may be less prone to produce atherosclerosis.

Modifications of the features of pulsatile flow which may be expected to retard the development of atherosclerosis are: (1) a slower pulse rate, (2) a slower rate of change of blood velocity from minimum to maximum, (3) a decreased peak velocity, (4) a decreased mean velocity, and (5) a smaller range of blood velocity.

The velocity of blood flow is largely determined by the contractility of the myocardium (vis a tergo) and the peripheral resistance.

It is notable that the absolute pressure in a hydraulic system does not determine the velocity of flow. The velocity of flow is determined by a gradient—the difference in pressure between two points in a continuous system. If there is no difference in pressure between two points, there is no flow, regardless of the absolute pressure present. Thus, a reduction in the difference in pressure (gradient) will decrease the velocity of flow between two points in a continuous hydraulic system. Locally as well as generally, if these hydraulic conditions, namely, a decreased blood velocity and decreased gradient, can be achieved without impairing other metabolic requirements of the body, the development of atherosclerosis may be minimized or retarded.

SUMMARY AND CONCLUSIONS

The development of atherosclerosis is a sequel to the forces of blood flow and is found in varying degrees of severity in all individuals at sites of predilection in the circulatory system characterized by diminished lateral pressure in accordance with the effects of the laws of fluid mechanics. The effect of the laws of fluid mechanics is the primary causative or etiologic factor for the development of atherosclerosis. Atherosclerosis may be considered the reactive biologic response of the arteries to the forces generated by the flowing blood.

Pulsatile flow, as found in the circulatory system, is characterized by hydraulic features and specifications which are more conducive to the production of atherosclerosis than steady flow.

It is notable that within physiologic limits, a slower pulse rate, a lower average blood velocity, a lower peak velocity, a lower rate of change in velocity, a decrease in peak contractility of the heart, and a decrease in pulse pressure are hydraulic conditions which may be expected to minimize or retard the development of atherosclerosis.

The reparative response of the intima at the cellular level to the forces of flowing blood (the biologic factor) should be further explored as another approach to control of the atherosclerotic process.

Atherosclerosis cannot be cured in the sense of curing an infectious disease. We may look forward to the control or modification of the relevant hydraulic factors which cause atherosclerosis. We may then retard

the rate of development of atherosclerotic vascular disease and consequently extend the human life span.

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Neurogenic Factors in Pathogenesis of Coronary Heart Disease

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Physicians understand that neurogenic factors play a major role in altering functions of the cardiovascular system such as heart rate, blood pressure, and peripheral vasculature, and as early as the eighteenth century it was recognized that emotional factors play a role in the symptomatology of coronary heart disease.[44, 66] About a century after Heberden presented his treatise,[44] Osler[62,63] stated that his patients with angina exhibited overt behavior that was sufficiently characteristic as to permit a presumptive diagnosis of coronary heart disease in a new patient simply by his external mannerisms as he entered the consultation room. This implied that organic change in cardiovascular structure could be ascribed to neurogenic factors and specifically that emotional factors might play a pathogenetic role in coronary atherosclerosis and clinical coronary heart disease. This concept was neglected, in spite of Osler's observations, until many years later when psychiatrists such as the Menningers,[57] Dunbar,[12] and Kemple[51] studied patients with coronary heart disease and emphasized the frequent exhibition of a strongly aggressive, hard-driving and goal-directed personality. These personality traits received so little attention that Gertler and White[35] avoided attributing causal relevance to the hard-driving, goal-directed behavior they observed in their study of 100 young patients with coronary heart disease, despite the fact that almost half the patients worked excessively and without adequate vacation periods, while only 12 per cent of their control subjects functioned similarly.

Our own group became interested in this field about 1955 since the pertinent literature showed that, despite the apparent *associational* relationships between the incidence of coronary heart disease and factors such as diet, serum lipids, cigarette smoking, physical inactivity, and heredity, there were enough exceptions to indicate the possible presence of

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other important etiologic factors.[11] Bronte-Stewart et al.,[2] in Cape Town, had observed that as good a correlation could be seen between variations of occupational responsibility and the varying incidence of coronary heart disease, as that seen between the different incidences of coronary heart disease in three population groups and the different dietary fat intakes. It also was apparent that there were fourfold or greater differences of coronary morbidity rates at the same dietary intake levels.[90] Isolated primitive societies[83] exhibited low serum lipids and freedom from coronary heart disease, despite habitual ingestion of diets high in saturated fats, and the same serum lipid–dietary fat disparity was observed in prison inmates.[36, 43] Moreover, prospective studies have not shown dietary differences between subsequently victimized subjects and those remaining free of coronary heart disease.[64] It also was clear that members of any group habitually ingesting a diet high in fats exhibited marked variability in serum lipids and lipoproteins, with little or no correlation between serum lipid levels and dietary intake, including that of saturated fats.[59] Indeed, the striking rise in the incidence of coronary heart disease witnessed in recent decades has not been accompanied by any parallel change of diet.[87] Kahn[49] found that "serum cholesterol changes associated with changes in dietary fat have not been very great in this country for the past 50 to 60 years. This in turn indicates that the increased risk of coronary heart disease . . . over this period is not related to dietary fat changes to a very important degree. . . . Other environmental factors are more probably associated with having raised the risk . . . to the present level." Also, it was clear that the coronary morbidity was astonishingly low in earlier decades of this and the past century among a host of older individuals in Britain and in the United States who also ingested an abundantly fat-enriched diet and who also indulged in little physical activity.[58] Finally, the recent increased incidence of coronary heart disease has occurred far too rapidly to incriminate altered heredity. Thus the roles of physical inactivity[33] and the saturated-fat content of the diet[69] in the pathogenesis of coronary heart disease have recently come under increasing criticism.

The classic risk factors enhancing the incidence of coronary heart disease are now well known. However, only a minority of individuals with such attributes in any prospective study have been victimized with the passage of time.[71] A considerable rate of coronary heart disease also was observed in individuals who did not exhibit many of these risk factors.[70, 72] More recently Keys et al.[52] showed that the classic risk factors account for only about half of the cases of coronary heart disease.

Definition, Prevalence, and Detection of Type A Behavior Pattern

In view of the above observations, we began to "re-see" younger subjects with coronary heart disease in order to discover whether they did or did not exhibit any characteristic emotional traits. It gradually became apparent that most patients with coronary heart disease under the age of 60 years did exhibit a particular set of emotional traits which we now term the *Type A Behavior Pattern.*

The Type A Behavior Pattern is a particular action–emotion complex which is exhibited by an individual who is engaged in a relatively *chronic*

and excessive struggle to obtain a usually excessive number of things from his environment in too short a period of time or against the opposing efforts of other things or persons in this same environment. This habitual struggle may consist of attempts to achieve or to do more and more in less and less time, or of a *chronic* conflict with one or a group of persons, either by preference or necessity. The person with a Type A Behavior Pattern rarely despairs of losing the struggle and thus differs from the subject suffering from a classic anxiety state who, on finding his challenges overwhelming, seeks therapeutic counsel. The Type A person thus advances to overcome his challenges while the subject with anxiety may retreat before his. The Type A individual exhibits enhanced personality traits of aggressiveness, ambitiousness, and competitive drive, is work-oriented, is often preoccupied with deadlines, and exhibits chronic impatience and usually a strong sense of temporal urgency. Type B individuals are mainly free of such *enhanced* personality traits and feel no pressing conflict with either time or other persons, and accordingly are free of any habitual sense of urgency.

Our contemporary environment has encouraged Pattern A behavior because it appears to offer special rewards to those who can perform *rapidly* and *aggressively*. Moreover, with increasing urbanization, technological progress, and density of population, our civilization presents challenges never experienced by earlier, less time-conscious generations.[88] Pattern A does not *solely* stem from an individual's personality but emerges when certain *challenges or conditions* of the milieu arise to elicit this complex of responses in susceptible individuals. If the challenges of the milieu were removed, it is quite possible that an already present Type A Behavior Pattern might lessen or even disappear. We have not observed any particular correlation between job or position and any particular type of behavior pattern. Other investigators also were not able to correlate industrial position to the prevalence of coronary heart disease.[53, 60, 64, 66]

We have described the methodology that we have found useful to delineate the behavior pattern.[73] The general appearance* and characteristic motor activities (brisk and impatient body movements, fist clenching in ordinary conversation, taut facial musculature, explosive and hurried speech patterns, lack of body relaxation, etc.) usually make the detection of this behavior pattern relatively easy. In a structured interview,[73] the subject is asked about 25 questions dealing with the degree of intensity of his (1) ambition, (2) drive, (3) competitive, aggressive and hostile feelings, and (4) sense of temporal urgency. In assessing the behavior pattern we are more interested in the *manner* in which the interviewee responds than in the *content* of his answers. When such interviews are tape-recorded, it has been found[6, 46] that a high degree of replicability can be obtained by independent observers.

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*Osler[62, 63] actually was describing what we now have labelled the Type A subject when he pointed out that his typical patient with coronary heart disease was "not the delicate, neurotic person...but the robust, the vigorous in mind and body, the *keen and ambitious man, the indicator of whose engine is always at 'full speed ahead'*!" (italics added).

Relationship of Type A Behavior Pattern to Prevalence and Incidence of Coronary Heart Disease

The significant association of Type A Behavior Pattern in both sexes with increased prevalence of coronary heart disease found in our early studies[15, 78] has now been confirmed by several observers,[7, 34, 68] and other investigators[4, 37, 41, 55, 56, 82, 85] also have found that the prevalence of coronary heart disease is increased in subjects who exhibited personality traits or environmental challenges similar to those shown by Type A subjects. The role of psychosocial factors in the pathogenesis of coronary heart disease has been extensively reviewed by Jenkins.[47]

In order to determine if Pattern A bears a prognostic relationship to coronary heart disease we initiated the Western Collaborative Group Study (WCGS)[73] in 1960–1961. Over 3500 men, aged 39 to 59 years at intake, were enlisted in this prospective study. Medical and socioeconomic histories; dietary, drinking and smoking habits; blood pressure; serum cholesterol, triglycerides and lipoproteins; blood clotting studies; anthropometric measurements; and assessment of behavior pattern were obtained. The data from annual follow-up surveys have been presented in a number of reports.[16, 70-80]

During 8½ years of follow-up[76, 77] in which clinical coronary heart disease occurred in 257 initially well men, it was found that initially well subjects assessed at intake as exhibiting the Type A Behavior Pattern have been more than twice as prone to develop clinical coronary heart disease (see Figure 1) as the subjects originally assessed as Type B. Moreover, Type A subjects were five times more prone to have a second myocardial infarct (see Figure 1) than were Type B subjects during this 8½ year interval. Submission of the data to multivariate analysis[44] indicated that, while the presence of Type A Behavior Pattern in men with other risk factors (e.g., hypertension, hypercholesterolemia, positive family history) further increased the incidence of coronary heart disease, nevertheless, Pattern A alone and independently appeared to exert a strong pathogenetic force.

We were able to examine the necropsy protocols and often microscopic sections of coronary vessels of 51 of 80 subjects who had died between 1960 and 1967, 25 of whom had died of coronary heart disease.[16] Twenty-two of these 25 deaths (88 per cent) had occurred in subjects with Type A Behavior Pattern. Not only 6 times more Type A than Type B subjects had died of coronary heart disease, but whether Type A subjects died of coronary heart disease or of some other illness or accident, their degree of coronary atherosclerosis was approximately twice that of Type B subjects.

These studies suggest that a close association exists between Type A Behavior Pattern and the pathogenesis of coronary heart disease. The data obtained by Caffrey[7] and by Quinlan et al.[68] in their study of monks, the statistical analyses of Cassel[10] done on the studies of Keith et al.,[50] the findings of Ganelina,[34] and findings in a population of twins[55, 56] in part confirm this association. The findings of Brozek, Keys, and Blackburn[3] in their prospective study of a group of Minnesota business men are also relevant since a significantly higher incidence of coronary heart disease was observed in men who exhibited clear-cut characteristics of Pattern A.

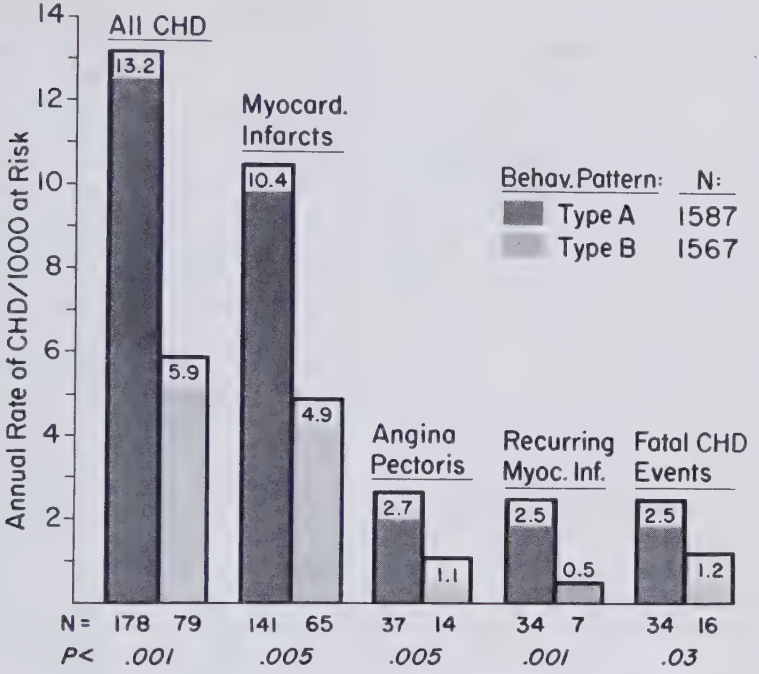

Figure 1. The annual rate of coronary heart disease in 3154 subjects studied prospectively in the Western Collaborative Group Study for 8½ years. The higher incidence of all expressions of coronary heart disease in the Type A subjects is shown. N equals number of cases. (*From* Rosenman, R. H., et al.: The central nervous system and coronary heart disease. Hospital Practice, 6:87–97, 1971, by permission.)

Clinical and Laboratory Studies in Type A Subjects

If Pattern A bears a causal relationship to coronary heart disease, then Type A persons should exhibit the biochemical derangements which are found in many patients already ill with coronary heart disease. In 1957 we determined the average serum cholesterol and blood clotting times of 42 accountants biweekly for approximately 6 months, beginning in January.[17] The average serum cholesterol rose and clotting time accelerated in association with occupational deadlines. This hypercholesterolemic effect of an environmental situation inducing even a temporary occurrence of Pattern A behavior has been repeatedly confirmed by other investigators.[11, 38, 67, 86, 89] We also found that the average serum cholesterol of both men[15] and women[78] who *chronically* exhibited Behavior Pattern Type A was significantly higher than that of Type B counterparts.

The majority of subjects exhibiting a *fully developed* Type A Behavior Pattern, when compared with subjects exhibiting *fully developed* Type B Behavior Pattern, were found to have not only a significantly greater fasting but also a higher postprandial serum triglyceride than their Type B counterparts.[18, 19, 81] Most such relatively hypertriglyceride-

mic Type A subjects also exhibited prolonged postprandial sludging of red blood cells, as observed in their bulbar conjunctival blood vessels for many hours after the ingestion of a meal which was rich in *either* saturated or unsaturated fat.[18] The relative hypertriglyceridemia observed in the majority of fully developed Type A subjects is associated with an elevation of serum prebetalipoproteins,[19] but not with any abnormality of plasma free fatty acid values, either before or after the ingestion of a fat-rich meal.[18, 29] The association of psychological traits with serum lipid levels has been reviewed by Jenkins et al.[48] and Levi,[51] and the elevated serum lipid-lipoprotein levels observed in men with Pattern A characteristics such as enhanced drive, ambitiousness, and aggressiveness has been well documented.[8, 42, 43, 48, 84]

Glucose metabolism was studied in groups of Type A and Type B men and no differences were observed in average plasma concentrations, either fasting or after a glucose load, and the average plasma uric acid concentrations of both groups of subjects were found to be approximately the same.[21] On the other hand, most *well developed* Type A subjects did exhibit[21] a hyperinsulinemic response to glucose ingestion. However, the data suggested that this hyperinsulinemia could not be causally responsible for the hypertriglyceridemia which also was observed in these same subjects.

We have studied the hypothalamic-pituitary-adrenal system of Type A men since emotional factors are highly related to this axis.[54] The average plasma cortisol and thyroxine values of Type A subjects were found to be similar to those of Type B subjects.[22, 54] However, when fully developed Type A subjects were challenged with large doses of corticotropin (ACTH), most of them excreted significantly less 17-hydroxycorticosteroids than Type B subjects.[23] This suggested the possibility that Type A subjects might be subject to a previous, long-standing as well as contemporary excess discharge of ACTH. The results of such a study[24] indicated that fully developed Type A men differed from a group of Type B subjects in exhibiting a somewhat higher level of plasma corticotropin throughout their waking hours. It is of interest that administration of corticotropin was found capable of temporarily abolishing the elevation of preprandial and postprandial serum triglycerides observed in fully developed Type A men but that a similar response was not induced by hydrocortisone.

Plasma growth hormone levels also have been determined in paired groups of Type A and Type B men. Not only was the average fasting plasma growth hormone of a group of *fully developed* Type A subjects found[21] to be significantly lower than that of *fully* developed Type B subjects, but also the growth hormone response of Type A subjects to arginine infusion, when tested during working hours, was significantly less than that of Type B subjects.[25] In view of the fact that the presence of growth hormone appears necessary for maintenance of a normal plasma cholesterol concentration,[26] the question arises whether the hypercholesterolemia so frequently seen in *fully developed* Type A subjects might be related to their apparent functional deficiency in growth hormone. It is significant that administration of growth hormone to hypercholesteremic Type A men induces a prompt, albeit temporary, significant fall of serum cholesterol.[32]

Although the random urinary corticoid excretion of *fully developed* Type A subjects does not differ from that on control Type B subjects, the urinary excretion of norepinephrine and 3-methoxy-4-hydroxymandelic acid was significantly increased during their daytime working environment.[5, 22] This last observation was confirmed by Carruthers.[8, 9] Nestel et al.[61] found that patients with angina pectoris excreted more catecholamines—a phenomenon which, they suggested, might be due to the personality rather than the CHD of their patients. These results present the possibility that this increased discharge of norepinephrine, which appears to be as characteristic of most *fully* developed Type A subjects as their relative hypercholesterolemia, may be more participatory than the latter phenomenon in the pathogenesis of coronary heart disease.[54] It is significant that in current studies we are observing that Type A subjects exhibit elevated plasma norepinephrine levels and enhanced secretion of norepinephrine in response to a milieu challenge test in comparison to Type B subjects.

Experimental Studies of the Role of the Central Nervous System in the Regulation of Serum Lipids

It would seem pertinent to report briefly on accumulating *experimental* evidence linking the central nervous system to lipid metabolism. In an early study[39] we found that chronic stimulation of the ventromedial nucleus of the hypothalamus of cholesterol-fed rabbits significantly elevated plasma cholesterol levels. This hypercholesterolemic effect of either hypothalamic stimulation[40] or injury[1] has been confirmed. Since exposure of rats and rabbits to auditory stress has been shown to alter pituitary,[91] adrenal,[13] or pituitary-adrenal[45] function and this response involves the hypothalamic area of the central nervous system,[45] it was of interest that enhanced alimentary hyperlipemia was induced in rats and rabbits by exposing them to a continuous auditory stimulus of "white" noise.[27] An involvement of the adrenal gland in the lipemic response to auditory stimuli was also suggested by the finding that such stimuli induce a marked increase of adrenal corticosteroid secretion,[45] and such increased secretory activity may persist for some weeks after exposure to such auditory stimuli.[13]

Alimentary lipemia also was studied in rats caged under a different environmental milieu. Rats housed in the midst of the busy laboratory milieu exhibited marked alimentary hyperlipemia that was considerably diminished when the animals were caged separately, and was largely prevented when they were housed in a soundproofed, unvisited room.[28] Removal of the adrenal glands and the hypophysis did not abolish the milieu-induced postprandial hyperlipemia of the fat-fed rat.[28] However, an electrolytic lesion placed in the anterior hypothalamus of similarly fat-fed rats prevented the milieu-induced postprandial hyperlipemia that was otherwise observed in these animals.[29]

Hypercholesterolemia was induced in rats by bilateral injury of the ventral medial nuclei, the fornices, and the medial portion of the lateral hypothalamic nuclei,[30] but could not be ascribed to any change in function of the thyroid, adrenals, testes, or pituitary that might have been induced by the hypothalamic lesion; nor could it be ascribed to any induced derangement of pancreatic discharge of insulin.[31]

These results clearly indicate that stimuli arising in the central nervous system can and do affect lipid metabolism of the rat and rabbit. The experimental, neurogenically induced enhancement of postprandial hyperlipemia is strongly reminiscent of that observed in Type A subjects[18-20] and it seems clear that the central nervous system is involved in the metabolism and regulation of the serum lipids.

SUMMARY

The factual data dealing with the relationship of the Type A Behavior Pattern to the incidence of coronary heart disease have been described. Epidemiologic findings indicate a strong association between Pattern A and the prevalence and incidence of coronary heart disease. Epidemiologic, clinical, and experimental data strongly suggest that this relationship is a causal one. It would appear that neurogenic factors play an important role in the pathogenesis of coronary artery disease and that intensified studies of such factors should be undertaken.

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Genesis of Atherosclerosis in Swine Fed High Fat-Cholesterol Diets

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In clinical medicine we have been aware of the complications of atherosclerosis for centuries. Autopsy studies carried out when complications prove to be fatal have provided a wealth of information on the late stages of the atherosclerotic process. Any second-year medical student can describe the narrowed arterial lumen, the thickened wall, the irregular intimal surface, and the gruel-like material that becomes apparent on cross-sectioning the lesions. Light microscopy and chemical studies have shown that these advanced atherosclerotic lesions contain much lipid, particularly cholesterol and its esters, as well as necrotic debris, collagen, mucopolysaccharides, elastic fibers, and numerous cells (Fig. 1). In our western society this type of lesion is very common in middle-aged and elderly people. It is much less common in young adults and rare in children. We will refer to this lesion as the necrotic lesion of atherosclerosis.

The type of arterial lesion that is common in young adults and at least present in children narrows the lumen only to a moderate degree, has a smooth intimal surface, and on cross-section shows little or no gruel and necrotic debris. By microscopy this type of lesion contains large numbers of smooth muscle cells with variable amounts of lipid in their cytoplasm (Fig. 1). Also present are large amounts of collagen, elastic fibers, and mucopolysaccharides. Microscopic foci of extracellular lipid and necrotic debris are found but are not a prominent feature. This lesion will be referred to herein as the proliferative lesion of atherosclerosis.

Abundant evidence indicates that the necrotic lesions develop from the proliferative lesions.[2] However, proliferative lesions do not inevitably become necrotic lesions, since the former may be found even in nonagenarians.

The genesis of the proliferative lesions in man has not been clearly

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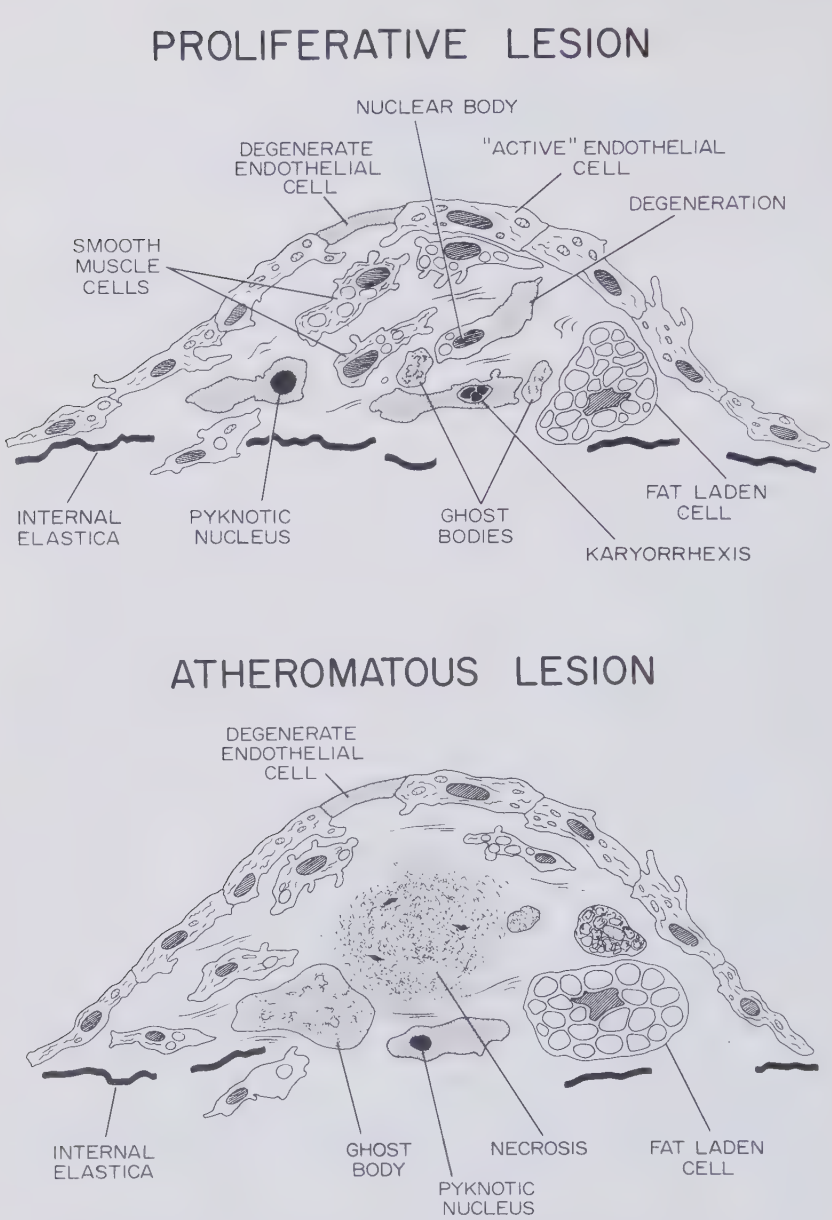

Figure 1. *Above*, Schematic illustration of the microscopic features of proliferative atherosclerotic lesions. The proliferative lesion is characterized by an accumulation of cells within the intimal space. Nearly all of the cells that can be identified with certainty by electron microscopy appear to be smooth muscle cells, although some are so laden with lipid that it is not possible to determine what kind of cells they are. Some of the intimal smooth muscle cells are dead or degenerating. Mucopolysaccharides and small elastic fibers are present, as well as collagen. Masses of fibrin are seen in some lesions. Occasional endothelial cells overlying the proliferative lesion display degeneration or death, while the remaining endothelial cells appear active. *Below*, an advanced necrotic lesion. The most characteristic feature of the necrotic lesion is a mass of lipid-rich necrotic debris in what is otherwise a proliferative lesion.

elucidated. They occur in all peoples regardless of diet, exercise, or any other known factor. They are more common around orifices of arterial branches, so it has been postulated that hemodynamic factors play a role. They may be produced by almost any type of injury, such as irradiation. However, they are seldom extensive and seldom develop into necrotic lesions unless the individual is on a high fat-cholesterol diet such as that eaten by most North Americans.

PROLIFERATION AND DEATH OF ARTERIAL SMOOTH MUSCLE AND ENDOTHELIAL CELLS

Proliferative lesions can be produced in swine by high fat-cholesterol diets as well as in several other species of experimental animals.[16] These lesions are similar in most respects to those in man and in time will develop into necrotic lesions.

We have been using swine fed high fat-cholesterol diets as a model for the study of the genesis of atherosclerosis induced by such diets.[3] Information obtained from this model is very likely to apply as well to man; but one should keep in mind that the pertinence for man has not as yet been directly proved. Also, though in most of the experiments to be described the only difference in experimental design between experimental and control swine is diet, this does not mean that diet is the only factor involved in the production of atherosclerotic lesion. For example, hemodynamic forces are obviously operating and may well act to modify effects of the diet. Immunologic factors may play a role. Also, endogenous chemical factors may be constantly operating in all animals, and these may result in injury and death of some smooth muscle cells and endothelial cells and proliferation of others; the effect of these factors may be intensified by diet.

However, regardless of the multiplicity of factors that may be involved in atherogenesis, an experimental situation can be created with swine in which diet is at least the precipitating factor. Young swine fed a high fat-cholesterol diet all develop some gross atherosclerotic lesions in a month or two while controls seldom if ever develop any gross lesions in the same period.[19] Thus, an experimental situation exists in which the genesis of atherosclerosis can be studied, regardless of the multiple factors that may be involved.

We postulated that the interaction between diet-related factors (cholesterol per se or other) and the arterial wall would begin long before the development of gross lesions. Identification and study of the postulated early changes prior to development of gross lesions could ultimately provide information that might aid in devising rational preventive measures. Pathogenetic mechanisms might be easier to elucidate if information regarding very early changes were integrated with knowledge of changes in gross lesions. In grossly visible lesions many complex metabolic changes are observed, and it is exceedingly difficult to separate cause from effect.

Attempts to obtain information prior to development of gross lesions by light microscopy studies of the arterial wall in swine fed high fat-

Table 1. *Composition of Diets Used in Swine Experiments with Amounts Consumed per Day in Grams*

Ingredients	Stock (PS)	Mild (PSC)	Severe (TSC)	Moderate (SC)
Casein	143	143	95	160
Sucrose	227	227	140	215
Butter	57	57	87	200
Peanut oil	57	57	87	40
Salt mix, Wesson	30	30	30	32
Vitamin mix	12.5	12.5	12.5	24
Choline chloride	2.5	2.5	2.5	4
Cellulose	121	113	24.5	82
Cholesterol	0	8	14	22
Sodium cholate	0	0	7	11
Propylthiouracil	0	0	0.5	0
Total	650	650	500	800
Calories	2506	2506	2506	3700

cholesterol diets such as the one shown in Table 1 were not very rewarding. Very small proliferative lesions not seen grossly could be found occasionally as early as 3 weeks after beginning the diet, but they did not appear significantly different from the slightly larger grossly visible lesions.[19] In theory this accumulation could result from (1) an increased rate of multiplication of smooth muscle cells, or (2) a decreased death rate of smooth muscle cells or (3) migration of smooth muscle cells from the media. Tritiated thymidine can be used to determine the percentage of cells synthesizing DNA at any one time and colchicine can be used to determine rate of entry into mitosis. Both types of study in swine as well as in any other species have indicated that there is excessive multiplication of smooth muscle cells in gross proliferative lesions as compared to rates in grossly normal arteries. The multiplication rate of smooth muscle cells in lesions is usually many-fold greater than in normal arteries. We have shown the same to be true for endothelial cells that lie over the proliferating smooth muscle cells and have concluded that the endothelial cells represent the surface component of the lesion.

Table 2. *Ratios of Chemical Determination of in vitro ^{3}H-Thymidine Incorporation of Abdominal Aorta of Swine Fed a High Fat-Cholesterol Diet up to 2 Weeks*

Days on diet	Serum cholesterol (mg. per 100 ml.) chol./stock	DPM ratio chol./stock
3	162/125	1.47
7	233/108	2.19
13	158/112	1.65

Table 3. *Mitotic Counts of Aortic Trifurcation Region of Swine Fed Cholesterol for Three Days, Expressed as Numbers of Mitoses per 10^4 Cells per Hour*

	CHOLESTEROL	CONTROL	P VALUE*
Endothelium	2.3	1.1	< .01
Subendothelial intima	3.2	1.5	< .01
Inner media	4.0	1.9	< .01

*Mann-Whitney U-test

It occurred to us that the ^{3}H-thymidine incorporation and colchicine-collection of mitoses techniques might be used in demonstrating changes that occur prior to development of gross lesions. In an early study we compared ^{3}H-thymidine incorporation into aortic DNA in swine fed a mild diet similar to that in Table 1 for intervals from 1 to 112 days, with that in controls.[19] Incorporation rates were demonstrated to be greater than that in controls even in the first week on diet (Table 2).

We then concentrated on the third day after beginning a high fat-cholesterol diet and found, using the colchicine technique, that rate of entry of arterial smooth muscle cells into mitosis was significantly greater at this time than in control.[1] The increase averaged approximately two-fold and hence was lower than the many-fold increase observed in lesions, as might be expected. Also the increase appeared to occur at random throughout the arterial wall instead of being localized to the intima and inner media where gross lesions appear (Table 3). It is notable that no increase in cholesterol concentration in arterial walls has been demonstrated at this time on diet although the serum concentration has increased from 100 to approximately 150 mg. per 100 ml.

In another study of *en face* preparations of arterial endothelium by ^{3}H-thymidine techniques in swine fed high fat-cholesterol diets for 3 days, two-fold or more increases in rate of incorporation as compared with controls were observed. Similar studies after one day on diet showed no changes[5] (Table 4).

Table 4. *^{3}H-Thymidine Radioautography on* en face *Preparations of Endothelial Cells of Aortic Trifurcation Region of Swine Fed Cholesterol for 1 or 3 Days, Expressed as Number of Labeled Cells per 10^4 Cells*

DAYS ON DIET	NO. OF PAIRS OF ANIMALS	CHOLESTEROL GROUP	CONTROL GROUP	P VALUES*
1	5	57	57	N.S.
3	9	149	71	< .001

*Chi square test

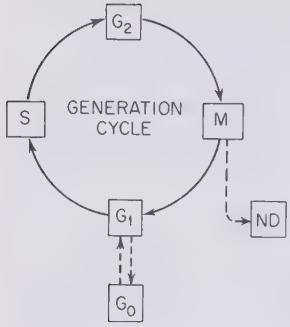

Figure 2. The cell cycle. M, mitosis period; G_1, post-mitosis–pre-DNA synthesis period; S, DNA synthesis; G_2, post-DNA synthesis-premitosis period; G_0, potential dividers that may be stimulated to re-enter the generation cycle; ND, nondividers that are permanently incapable of dividing.

The above studies indicated that an early effect of the high fat-cholesterol diet in swine was to increase the overall rate of DNA synthesis and division in smooth muscle cells and endothelial cells of arteries long before the development of gross lesions. This led us to ask what change in the cell generation cycle had occurred that accounted for the change.[20] In Figure 2 is a stylized view of the cell cycle as generally viewed at the present time. In Table 5 is shown the available information on the cell cycle and dividing population of arterial smooth muscle cells prior to our investigation. Also shown is some of the information gained thus far in our studies.[20] The dividing population appears to include at least half and perhaps all of the smooth muscle cells in the arterial wall. There is no small rapidly dividing stem cell population such as that found in skin, bone marrow, and intestine. Retention of significant numbers of smooth muscle cells in the post-DNA synthesis, pre-mitotic period does not appear to occur. The results of our comparison of high fat-cholesterol and control swine suggest that the effect of the diet is to increase the rate of entry from G_1 and/or G_0 into DNA synthesis. Hence, the time spent in G_1 and/or G_0 is shortened. This information should permit the formulation and testing of more precise hypotheses regarding the molecular basis for the change than would otherwise be possible.

The above observations suggest that studies of control mechanisms for DNA synthesis and cell division of arterial smooth muscle cells

Table 5. *Information Surmised on Arterial Smooth Muscle Cells in Relation to Cell Cycle*

		BEFORE EXPERIMENT	AFTER EXPERIMENT
Cells in:	S	~ 0.7%	~ 0.7%
	G_2	< 1–98%	< 1%
	M	< 1%	< 1%
	$G_1 + G_0$	< 1–98%	50–98%
	Dividing population	2–98%	50–100%
	Non-dividing population	0–98%	0–50%
Generation time		?	> 28 days

should be made. In studies of skin and a few other tissues in several laboratories, extracts have been obtained that reduce cell division rates in vivo and in vitro in the cell of origin when given in small amounts (less than 1 mg. quantities).[1, 9, 17] Evidence has been presented suggesting that the effect is produced by a specific component, and the word "chalone" has been coined for the postulated component. Chalones described thus far appear to be tissue specific but not species specific. In work now in progress we are attempting to find out whether or not a chalone-like substance (or property) is present in arterial tissue. Preliminary studies suggest that such a substance is present and it is highly effective in reducing rates of division of arterial smooth muscle cells. However, very likely many years of study will be required before the implications regarding chalones for prevention or treatment of atherosclerosis for man, if any, are known.

Thus far in this report we have dealt exclusively with proliferative aspects of the genesis of atherosclerosis. Yet necrosis is a prominent feature of the advanced lesion.[6] Even in early proliferative lesions microscopic foci of necrosis are not uncommon. We wanted to find out how early this change appeared in the arteries of swine fed high fat-cholesterol diets. Light microscopy did not prove to be useful in this regard, so we turned to electron microscopy. Arteries of swine fed high fat-cholesterol or control diets were studied after 3 days on diet.[7] Ultra-structural changes suggesting individual cell injury or death were observed in all swine examined regardless of type of diet. These changes appeared qualitatively similar in the two groups. Thus it was necessary to do a quantitative study. Extensive counts were made of the various types of change that were observed in arterial smooth muscle cells and related to the total number of cells. Results indicated a significantly larger percentage of dead and damaged cells in the high fat-cholesterol than in the control group. These results cannot be translated into rates, since it is not known how long damaged and dead cells remain recognizable in the tissue. However, they strongly suggest that an increased rate of smooth muscle cell deaths occurs very early in the genesis of atherosclerosis.

The relations between increased rates of cell division and cell death in this situation are not known. In virtually all types of injury, cell proliferation begins shortly after cell death. However, it also seems likely that increase in rates of cell multiplication from whatever cause will be offset up to a point by increased death rates as part of the homeostatic system of the tissue. Also many types of cellular injury can result in either division or death, depending perhaps on the site and extent of the injury.

Many other aspects of metabolism that may be involved in the genesis of atherosclerosis are now being investigated. Gross proliferative lesions have increased rates of oxygen uptake[14] and protein synthesis,[3] as might be expected. Increased oxygen uptake compared to controls has also been found in the early period prior to gross lesions.[18] A general increase in protein synthesis has not been demonstrated in this early period; but studies of specific proteins such as collagen and elastin might be more rewarding. Studies of respiratory control and ADP/O_2 ratios in swine fed high fat-cholesterol diets have not shown significant differences either before or after gross lesions develop.[15] However, there has

been one study done in atherosclerotic rabbits that suggests the possibility of mitochondrial dysfunction.[22]

In Figure 3 we have summarized on a time scale some of the changes that have been demonstrated in swine fed high fat-cholesterol diets. Many further studies of arterial cellular metabolism and structure are needed before the genesis of atherosclerosis can be elucidated in its entirety even in the high fat-cholesterol fed experimental animal. However, as leads develop they should be investigated wherever possible for pertinence to man.

POSSIBLE MECHANISMS ACCOUNTING FOR INTERACTION BETWEEN HIGH FAT-CHOLESTEROL DIETS AND THE ARTERIAL WALL

One rather puzzling aspect of our studies of atherogenesis in swine is that in the period up to 1 month on diet we have not been able to demonstrate any increase in the concentration of cholesterol in arterial tissue.[13] With the diets commonly used, cholesterol levels in the plasma begin to rise in the first days and within 2 weeks begin to level off at approximately 200 to 250 mg. per 100 ml. (compared with 100 mg. per 100 ml. at the outset). After about 2 months on diet plasma levels are similar to those at 1 month and by that time we can also demonstrate by chemical

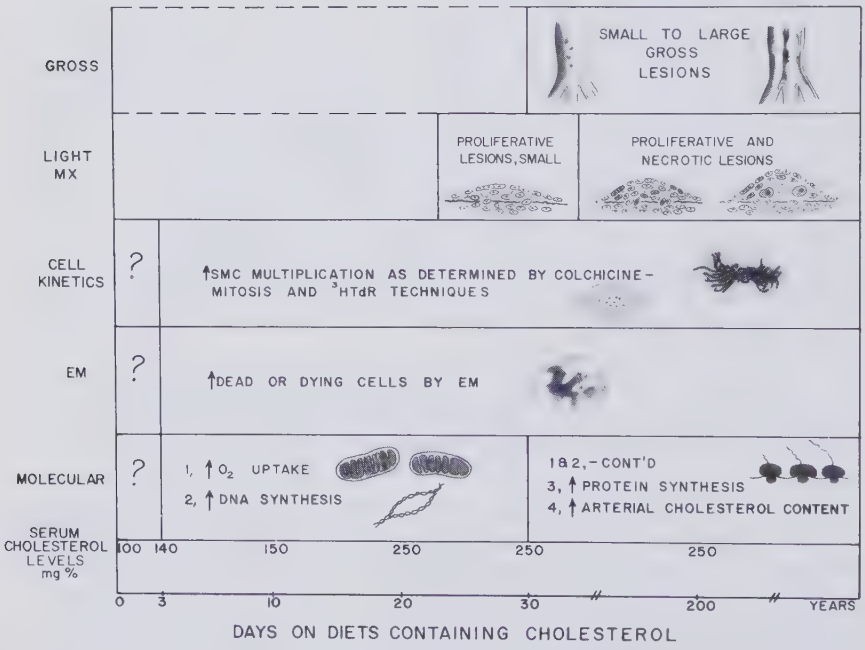

Figure 3. Summary on a time scale in days after beginning high fat-cholesterol diets of some of the metabolic and structural changes that occur in the arteries of swine as a result of the diet.

means small increases in the concentration of both free and esterified cholesterol in arterial tissue. Histologic examination of sections stained for lipid suggests that much of the increase is concentrated in foci near the endothelial surface and that these lipid foci are associated with excessive proliferation of smooth muscle cells, i.e., the development of proliferative lesions. It is not as yet known whether the focal accumulation of lipid occurs prior to or after the proliferative lesion begins. It is tempting to believe that the focal lipid accumulation occurs first and causes the focal cellular proliferation. On the other hand, it is well known that the endothelium over atherosclerotic lesions is much more permeable to lipids than is endothelium over normal tissue, so that the increase in lipid could be a secondary phenomenon.

It is also of interest that arterial smooth muscle cells in mitosis in the early period on diet prior to development of gross lesions show no lipid droplets either by light or electron microscopy.[8] Lipid droplets are absent even though the cells that have been stimulated to divide are undoubtedly present in substantial numbers as indicated by ^{3}H-thymidine and colchicine-collection of mitoses studies. These observations suggest several possibilities:

Perhaps there is really no increased lipid in the stimulated cells and the effect of the high fat-cholesterol diet is produced through indirect means. For example, the diet may produce its effect through inducing the production of some protein substance that in turn stimulates arterial smooth muscle cells to divide. As another example, the effect may be produced through neutralizing an already existing substance, such as a chalone that is circulating in the blood and that would otherwise affect the cells.

A second possibility is that increased amounts of cholesterol have been incorporated into some membranous components of the cell, resulting in alteration of the properties of the membrane. If this postulated change were focal, the overall increase might be too small to be detected by conventional techniques, hence accounting for failure to demonstrate increased concentrations prior to 2 months on diet.

A third possibility is that there is an increase in cholesterol in the soluble fraction of the stimulated cells but that it is too finely dispersed to be recognizable even by electron microscopy. In this form it might interact with other small elements in the cell to produce the observed effect.

POSSIBLE SYNERGISM BETWEEN HIGH FAT, HIGH CHOLESTEROL DIETS AND OTHER FACTORS

In another approach to the investigation of the genesis and progression of atherosclerosis we are investigating possible synergism of high fat-cholesterol diets and direct injury in the production of lesions. In an earlier study[21] a single low dosage of irradiation, given over the thoracic aorta of rabbits, was found to enhance the extent and severity of atherosclerosis induced by a high fat-cholesterol diet. The increase in atherosclerosis appeared to be due to an increased susceptibility of the arterial wall to the effect of cholesterol and not due to the summation of effects of

two variables. This enhancement was temporary, and did not appear to be due to a permanent alteration in some cellular component, such as the DNA of smooth muscle cells. In a more recent study, deep x-irradiation was given as a form of injury to coronary arteries of swine.[11] If swine are fed a high fat-cholesterol diet for a short time and then given two doses of irradiation to the heart the process of atherogenesis can be greatly accelerated (even though only minimal changes are produced by the same doses of irradiation when swine are on a low fat commercial mash diet). Within 4 to 6 months occlusive atherosclerotic lesions will have developed in coronary arteries of the high fat-cholesterol swine and most swine will have one or more myocardial infarcts. The swine usually show no outward signs of illness until moments before death; they are active, alert, responsive, have good appetites and are usually indistinguishable from controls. However, they are prone to sudden collapse and death within a few minutes (Fig. 4). The terminal episode may be precipitated by minor procedures, such as the recording of an electrocardiogram, or it may occur while the animal is undisturbed in his cage. We have considered this syndrome to simulate closely the sudden death syndrome in man. Terminal electrocardiograms have been obtained on 16 of these swine and all have died as a result of some type of cardiac arrhythmia, usually ventricular fibrillation[12] (Fig. 5).

It is unlikely that humans receive enough irradiation to accelerate the process of atherogenesis except in very unusual situations. However, there may well be many other forms of injury acting as accelerators that have not as yet been recognized.

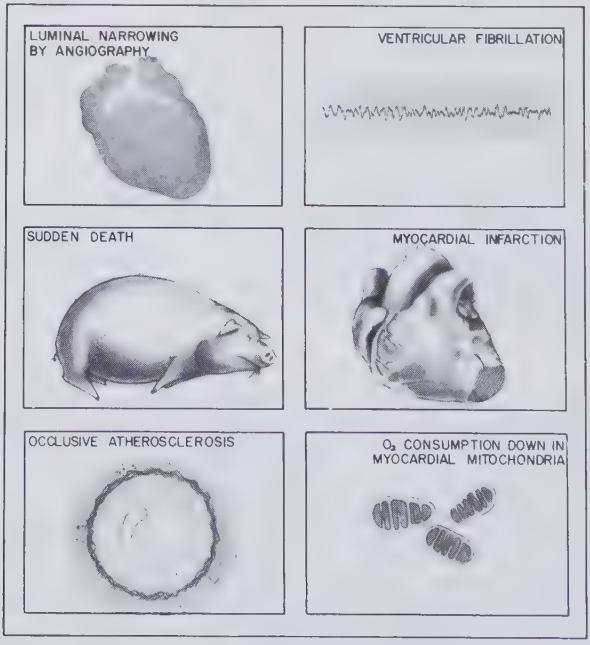

Figure 4. Some of the features associated with sudden death of swine with advanced coronary atherosclerosis.

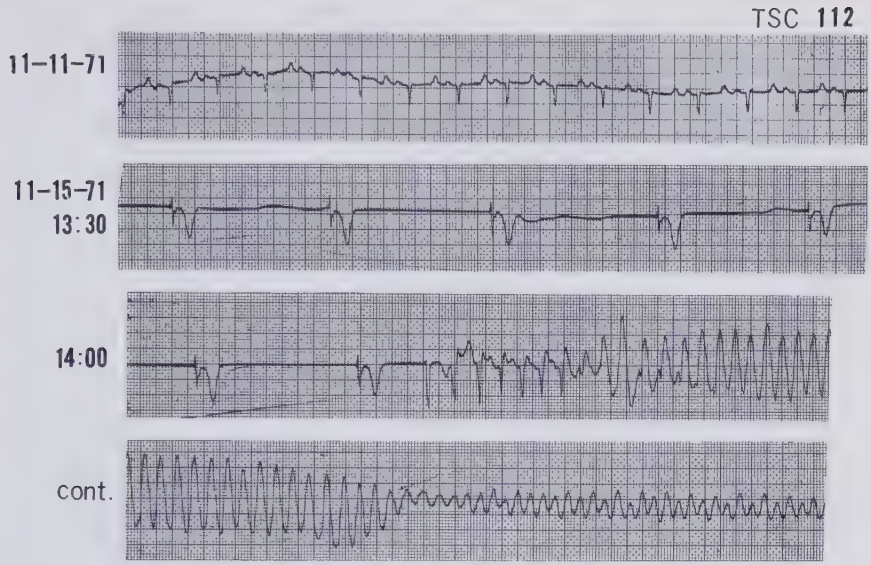

Figure 5. Electrocardiograms of a swine fed the severe atherogenic diet (Table 1) for 6 months and irradiated twice over the precordial region show sinus rhythm with deep Q wave on 11/11/1971. On 11/15/71 nodal rhythm developed and was followed by ventricular tachycardia and ventricular fibrillation.

CONCLUSION

The genesis and progression of atherosclerosis involve a complex interplay of metabolic, structural, and environmental elements. A few of the elements are well known but most are just beginning to be identified. Hopefully, advancing knowledge concerning the nature of the disease will lead to development of therapeutic and preventive measures that are more effective than those available at present.

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Vascular Enzymes and the Relevance of Their Study to Problems of Atherogenesis

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In 1962, when the present reviewer made his first attempt to review the literature on vascular enzymes[133] the task was relatively simple and almost all of the available data could be included. Comparatively little work had been done in this field at that time. Today, however, only a very subjectively selected fraction of the large number of available data can be given in a short review. For more detailed information the reader is referred to recently published monographs.[61, 136]

SOME GENERAL PECULIARITIES OF VASCULAR METABOLISM

Because of the specific properties of the arterial wall, it is very difficult to study the intermediary metabolism of this tissue by techniques that yielded excellent results in the study of organs such as the liver and heart. For example, previous attempts to measure oxygen consumption of arterial homogenates or intima-media preparations using the Warburg respirometer produced highly contradictory data mainly because of their low rate of respiration and need for prolonged incubations. With the use of the oxygen electrode, however, the sensitivity appears to be very much increased.[95] Great obstacles are encountered in the classical way of measuring oxidative phosphorylation because of the difficulty in preparing viable mitochondria from arterial tissue. Nevertheless, some basic properties of arterial tissue metabolism begin to unfold, thanks to the concentrated efforts of investigators in this field.

To be able to understand the rationale behind some of the enzyme studies, it will be useful to delineate briefly a few of these metabolic features of the vessel wall.

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Arterial Bioenergetics and Oxygen Supply

From the work of Kirk and co-workers,[64] Pantesco and co-workers,[101] and others, it appears that in contrast to most other tissues, arterial wall oxygen consumption does not exert a "braking" action on glycolysis; i.e., there is no Pasteur effect and the arterial wall manifests the phenomenon of "aerobic glycolysis." Data obtained by incubating surviving bovine and human vessels indicate that in the arteries only 3 per cent and in the veins 6.2 per cent of added glucose is metabolized through the Krebs cycle, and the remaining glucose is used mainly for the formation of lactate and incorporation into glycogen.[70-72] These and similar results would indicate that the energy needs of the vessel wall are supplied mainly by glycolysis. However, it is important to realize that in such incubation studies the perfusion of the vessels *via* the *vasa vasorum* is completely eliminated and hypoxia of the tissue necessarily results.

In addition, most of the published studies have been carried out using precooled tissue. It was recently shown[115, 116] that cooling decreases respiration of arterial tissue 5-fold while glycolysis is decreased by only about 50 per cent. Furthermore, it can be calculated that under conditions of aerobic glycolysis, even if the utilization of glucose by oxidation is only as low as 5 per cent, this still represents about 50 per cent of useful energy being provided by respiration. Slight increases of glucose oxidation above that level result in a substantial increase in the production of energy by oxidative phosphorylation.[116] It is interesting in this connection that if the normal artery is kept at 37° C. before glycolysis and tissue respiration is measured, only 40 per cent of ATP appears to be derived from glycolysis and 60 per cent from oxidative phosphorylation.[115, 116] Lactic acid production is also significantly lower in an oxygen than in a nitrogen atmosphere.[116] We can conclude that the artery, because of the low level of total energy supply, is vulnerable to further reduction in the oxygen supply. This is in agreement with recent findings, suggesting an essential role of hypoxic arterial damage in the pathogenesis of atherosclerosis.[65, 112]

Notes on Lipid Synthesis in the Artery

An interesting feature of arterial (and myocardial) metabolism seems to be that the "driving force" for fatty acid synthesis is different from other tissues. Fatty acid synthesis is a reductive process and in most tissues the hydrogens (or electron equivalents) originate from reduced NADP (TPN). However, according to Whereat,[131] in the artery the hydrogen donor is reduced NAD (DPN), instead of reduced NADP, and the driving force for fatty acid synthesis is the ratio of the reduced to oxidized form of NAD. This is important in view of what has been said above concerning the role of respiration in arterial metabolism.

The main producers of reduced NAD are reactions catalyzed by mitochondrial Krebs cycle enzymes, and the hydrogens (electron equivalents) have to be carried *via* the cytochrome system to oxygen, this being the process underlying oxidative phosphorylation. Consequently, impairment of electron transport to oxygen necessarily results in accumulation of reduced NAD. In fact, it could be demonstrated that impairment of

electron equivalent transfer from reduced NAD to the cytochrome system stimulated fatty acid synthesis by heart mitochondria. In rabbit aortas fatty acid synthesis occurs, according to Whereat, predominantly in the mitochondria, suggesting the same mechanism as found in the heart.[130, 131] It has to be added, however, that even if the "driving force" is the ratio of the reduced to oxidized form of NAD, transhydrogenases present in arterial tissue may transfer the hydrogen from NAD to NADP, and the immediate hydrogen donor for reductive synthesis may actually be reduced NADP.

Atheromatous arteries are able to synthesize cholesterol at an accelerated rate but this appears to be of minor importance in comparison with the increased influx of cholesterol into the artery in states characterized by hypercholesterolemia. (See reviews of Dayton and Hashimoto[22] and Zilversmit.[151]) There is evidence, however, that in the atherosclerotic artery cholesterol esters are derived by local synthesis and this may explain the different cholesterol ester composition of the artery and plasma. An alternative explanation is that the artery hydrolyzes preferentially some cholesterol esters, leading to differences in composition between plasma and artery. There is also ample evidence that the arterial wall is able to synthesize phospholipids, and in the atherosclerotic artery phospholipid synthesis is higher than in the normal vessel. Interestingly enough, more complicated lesions exhibit a high proportion of sphingomyelin. It would be, however, out of the scope of the present review to go into further details of lipid synthesis in arterial tissue.

Mucopolysaccharides and Lipoproteins

An interesting aspect of arterial metabolism is connected with the observation that serum beta and pre-beta lipoproteins *in vitro* form insoluble complexes with heparin and other sulfated acid mucopolysaccharides in the presence of Ca^{++} ions.[13] Gerö and his co-workers[8, 34] have demonstrated that this applies to aortic mucopolysaccharides and they believe that the main lipid-binding compound is heparitin sulphate. The complex formation and its mechanism has been thoroughly studied by Berenson and co-workers,[7, 19, 73, 121] Bihari-Varga et al.[8, 9] and others. It has been suggested that Ca^{++} acts as a bridge between N-sulfate groups of the mucopolysaccharide and phosphate groups of lipoprotein phospholipids.[121]

The question arises, of course, whether atherosclerosis is preceded or accompanied by qualitative or quantitative changes of arterial mucopolysaccharides. Suffice it to say that the reports in the literature are very controversial on this issue. Histochemical studies, based on increased metachromasia, were interpreted as an increase in mucopolysaccharide content. Chemical measurements gave conflicting results. A similar controversy exists regarding radiosulfate uptake into arterial mucopolysaccharides of animal or human atherosclerotic aortas. It is possible that changes in the affinity of mucopolysaccharides to lipoproteins are more connected with qualitative than quantitative alterations of mucopolysaccharides. The normal constituents appear to be hyaluronic acid, chondroitin-4 and 6-sulfate, heparitin-sulfate and dermatan sulfate. Although the mucopolysaccharides must not necessarily be changed in the athero-

sclerotic vessel, it appears that the concentration of the individual components changes independently in the aging or diseased artery.[111] In addition, physicochemical changes including depolymerization of mucopolysaccharides may take place, influencing not only the affinity toward lipoproteins, but also the permeability of the arterial wall. Perhaps aortic chondroitin sulfates are more heterogeneous than had been expected.

From these brief remarks it should be clear that in the search for the pathogenesis of atherosclerosis the metabolism of arterial connective tissue, including mucopolysaccharides, should not be neglected.

VASCULAR ENZYMES AND ATHEROGENESIS

Having given an overall picture of some spects of arterial wall metabolism, we can proceed to an outline of work done in the field of vascular enzymes and discuss what relevance some of the observations may have to atherogenesis. More detailed data are available in other publications.[61, 136] In the present review we will mainly describe results obtained by biochemical methods and no attempt will be made to give a detailed picture of data gathered by histochemical techniques. However, some investigators acquired a good deal of useful information by the histochemical approach. Therefore, a few data obtained by such techniques will also occasionally be mentioned. The histochemistry of vascular enzymes has been described in detail by Lojda,[86, 87] Sandner and Bourne,[113] Maier et al.,[90] Stavrou and Dahme,[122] and especially by Adams in his book on vascular histochemistry.[4]

It is reasonable to anticipate that most enzymes characteristic for all living matter will be found in arterial tissue. As far as specific metabolic pathways are concerned, the most completely investigated arterial enzymes are those of glycolysis and glycogen breakdown. Data on enzymes of the Krebs cycle, of the pentose phosphate pathway, of the polyol pathway,[17] and on enzymes of the terminal respiratory chain are also available. In addition to these enzymes there are also quite extensive data on many other enzymes; they are difficult to fit into generally accepted pathways, or have so far only been studied in the vessel wall independently from other related enzymatic reactions. Such enzymes are, for example, some enzymes of lipid synthesis and breakdown, enzymes of the glyoxalase system, enzymes of phosphorus metabolism, of connective tissue metabolism, and many oxidoreductases, aminotransferases, and especially hydrolases. Some of the latter enzymes, for example cathepsin, acid phosphatase, and all enzymes of mucopolysaccharide catabolism, are lysosomal enzymes, and it is assumed that their increased activity is connected with phagocytosis, cell injury, and cell death. Finally, enzyme cofactors, such as coenzyme A, glutathione, flavin nucleotides, nicotinamide-containing coenzymes, as well as thiamine, carnitine, vitamin B_{12}, and para-amino-benzoic acid, have been investigated in vascular tissue.[54, 57, 58, 62] Recently DNA and RNA polymerases were also studied in aortic nuclei.[56]

Effects of Age and Sex

The available data indicate that many arterial enzyme activities change with age. Most enzyme activities tend to be lower in the aortas or coronary arteries of children than in those of adults. However, over the age of 40 the activities of most vascular enzymes and cofactors again decrease. Some enzymes such as lactate dehydrogenase, 5–nucleotidase, acid phosphatase, ribosephosphate isomerase, all enzymes of mucopolysaccharide breakdown and phospholipases provide an exception by exhibiting a clear-cut rise in activities.[28, 60, 61, 69, 136]

It is also clear that some enzyme activities exhibit clear-cut sex-linked differences. For example, the activity of phosphatases is lower, and the activity of 5′–nucleotidase higher in female than male rat aortas.[96] Estrogen treatment of male rats results in corresponding changes in enzyme activities.[142] The experiments by Malinow et al.[91] and Mrhová and Zemplényi[96] clearly showed that gonadectomy also induces significant changes in the activities of many aortic enzymes. For example, in the aortas of castrated male rats the activity of alkaline and acid phosphomonoesterase, malate dehydrogenase, and probably also 5′-nucleotidase is higher than in the aortas of sham-operated animals. On the other hand, in gonadectomized female rats the activities of malate dehydrogenase and 5′-nucleotidase significantly decrease.

The results obtained by Kirk[59, 61] in human aortas indicate that male aortas display significantly higher activities of two NADP-dependent enzymes than female aortas, namely glucose-6-phosphate dehydrogenase and decarboxylating malate dehydrogenase; the activities of two other "reduced NADP-producing" enzymes (i.e., isocitrate dehydrogenase and decarboxylating phosphogluconate dehydrogenase) reveal a similar tendency. The same was observed for two of the above four enzymes in the male coronary arteries. Most interestingly the activity of glycerol-3-phosphate dehydrogenase is also significantly higher in male than female aortas.[63] Since reduced NADP is intimately involved in the synthesis of cholesterol and fatty acids and since glycerol 3-phosphate ("active glycerol") is the common acceptor of fatty acids in triglyceride synthesis, it is tempting to ascribe the above features of the male arteries to increased tendency toward triglyceride synthesis. However, other data are not so unequivocal concerning the role of glycerol-3-phosphate dehydrogenase. While in canine atherosclerotic aortas the activity of the enzyme is stated to be increased,[90] in experimental rabbit atherosclerosis[97, 144] and in human atherosclerosis[61, 63] it is lower than in normal arteries. However, it appears that in the dog experiments the mitochondrial flavoprotein enzyme ("Meyerhof-Green enzyme") has been studied, whereas in the human and rabbit aortas the cytoplasmic NAD-dependent "Baranowski enzyme" has been investigated.

ENZYME ACTIVITIES IN ATHEROSCLEROTIC VESSELS

With advancing atherosclerosis, most enzymatic activities and cofactor levels in human arteries tend to decline. As seen from Figures 1, 2, and 3, constructed according to data published by Kirk,[61] almost all of the

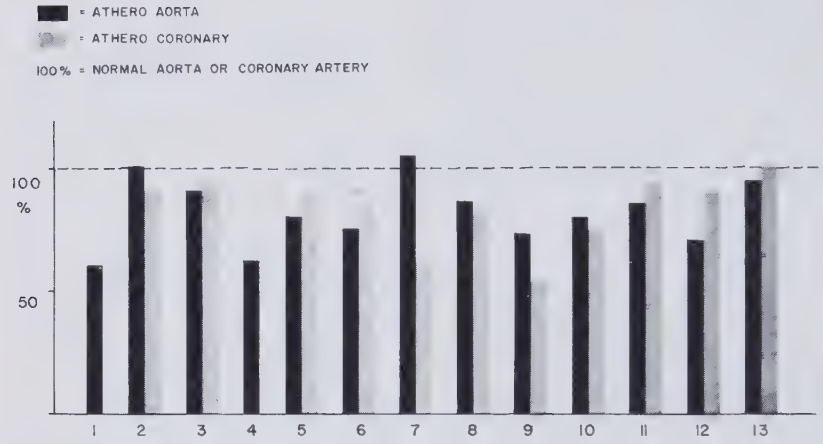

Figure 1. Differences between atherosclerotic and normal human arteries in activities of enzymes of glycolysis and of the glycogen pathway. 1, Aldolase. 2, Enolase. 3, Glyceraldehyde-3-phosphate dehydrogenase. 4, Glycogen phosphorylase. 5, Hexokinase. 6, Lactate dehydrogenase. 7, Phosphofructokinase. 8, Phosphoglucoisomerase. 9, Phosphoglucomutase. 10, Phosphoglyceromutase. 11, Phosphoglycerate kinase. 12, Pyruvate kinase. 13, Triosephosphate isomerase. (Constructed according to data from Kirk, J. E.: Enzymes of the Arterial Wall. New York, Academic Press, 1969.)

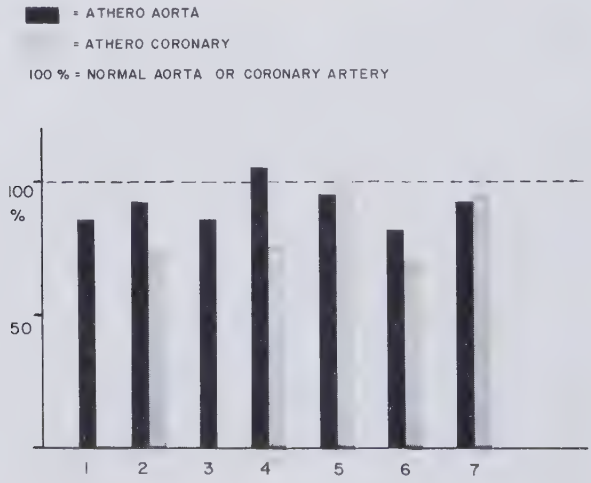

Figure 2. Differences between atherosclerotic and normal human arteries in activities of enzymes of the tricarboxylic acid cycle (Krebs' cycle) and some related enzymes(*). 1, Aconitase. 2, Citrate synthase. 3, Fumarase. 4, Glutamate dehydrogenase.* 5, Isocitrate dehydrogenase. 6, Malate dehydrogenase. 7, NADP-malic enzyme.* (Constructed according to data from Kirk, J. E.: Enzymes of the Arterial Wall. New York, Academic Press, 1969.)

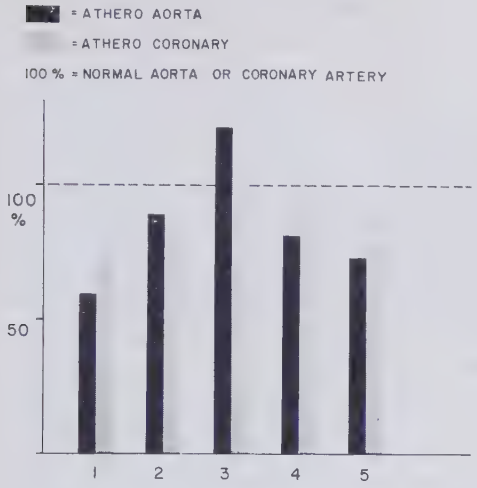

Figure 3. Differences between atherosclerotic and normal human arteries in activities of enzymes of the pentose phosphate pathway. 1, Glucose-6-phosphate dehydrogenase. 2, 6-Phosphogluconate dehydrogenase. 3, Ribose-5-phosphate isomerase. 4, Transaldolase. 5, Transketolase. (Constructed according to data from Kirk, J. E.: Enzymes of the Arterial Wall. New York, Academic Press, 1969.)

enzymes of the Krebs cycle studied so far, as well as those of the pentose phosphate pathway and many other enzymes, exhibit such a tendency in human aorta and coronary artery. Among the other enzymes, not shown in the above figures, carboxylic esterase, purine nucleoside phosphorylase, glutamic pyruvic transaminase, all enzymes of mucopolysaccharide breakdown (see later), acid phosphomonoesterase and cathepsin were found to manifest increased activity either in the atherosclerotic aorta, or coronary artery, or both vessels of man.[61, 69] It is, however, not possible to decide whether these changes in enzyme activities precede the development of atherosclerotic lesions or are secondary to the disease. This is, of course, a crucial problem in the search for the role of vascular metabolism in the pathogenesis of atherosclerosis.

Consequently, to get an answer to such questions, it appeared reasonable to study early stages of induction of different types of experimental atherosclerosis in animals. Maier and Haimovici[90a] have shown that aortic slices of rabbits and dogs subjected to an atherogenic diet exhibited a decreased cytochrome oxidase activity prior to the development of atherosclerosis, whereas the succinoxidase system and the esterase activity remained unchanged. In another series of experiments[144] it could be demonstrated that the earliest changes of aortic enzyme activities in experimentally induced atherosclerosis in rabbits (4 to 10 weeks on cholesterol feeding) were increases in the activities of alkaline and acid phosphomonoesterase, beta-glucuronidase, as well as declines in the activities of glycerol-3-phosphate dehydrogenase, lactate dehydrogenase, succinate dehydrogenase, and perhaps malate dehydrogenase.[136] Increased lipolytic activity[134, 138] appeared only in later stages of atherosclerosis. No significant changes in the activities of ATPase, 5′-nucleotidase, or glucose-phosphate isomerase could be detected.[144]

We will see later that similar changes of enzyme activities are characteristic in situations associated with vascular injury and with connective tissue reactions to injury. Do the changes just described in choles-

terol-induced atherosclerosis also represent reaction of the arterial wall to (metabolic) damage caused by cholesterol? We will return to this topic later.

It appears that an approach other than experimental atherosclerosis is more appropriate to answer the question whether changes of arterial metabolism precede the development of atherosclerosis. It is well known that different human arteries and even different segments of the same artery manifest a considerable variation in susceptibility to atherosclerosis. For example, the severity of atherosclerosis is decidedly higher in the abdominal than ascending aorta; or higher in the aorta than in the pulmonary artery; or higher in the femoral than the brachial artery. Such disparities provide a unique opportunity for investigation of "local" metabolic factors in atherogenesis.

The results that follow were calculated either on the saline-extractable protein content basis or on the deoxyribonucleic acid content of the vessels investigated. In all cases arteries or arterial segments from the same subjects were compared. Figure 6 shows that the activities of lactate, malate and succinate dehydrogenases as well as 5′-nucleotidase are higher in normal parts of the ascending aorta than abdominal specimens of the same human aortas. In contrast, the activity of acid phosphatase is higher in the abdominal than the ascending aorta. The same enzymes were studied in comparing activities in the femoral and brachial arteries or in comparing the thoracic aortas and pulmonary arteries. The results were very similar, except that either the activity ratio of 5′-nucleotidase was reversed or there was no difference between the specimens studied. The activities of Krebs cycle enzymes, especially malate and succinate dehydrogenases, were higher and the activities of acid phosphomonoesterase were lower in the relatively atherosclerosis-resistant (durable) arterial specimens.[136, 141, 146-148]

When results are calculated on the wet-tissue basis the activity ratios of Krebs cycle enzymes in the pulmonary artery *versus* aorta are the same as in the above studies. Kirk and his co-workers[61] very systematically compared in this way enzymatic activities not only in the human aorta and pulmonary artery, but also in the coronary arteries and vena cava. As can be seen in Figure 4*A*, all Krebs cycle enzymes that have been studied displayed a higher activity in the pulmonary artery and coronary artery than in the aorta. The phosphomonoesterase activities, on the other hand, were highest in the aortas. However, the ratio of enzyme activities of neither the glycolytic cycle (Fig. 5) nor the pentose phosphate shunt (Fig. 4*B*) manifested uniformity between the aorta and pulmonary artery, although in the coronary artery most glycolytic enzyme activities were lower than in the aorta. The activities of creatine phosphokinase and ATPase were higher in the pulmonary artery and coronary artery than in the aorta. This is probably due to higher actomyosin content of the former vessels. Klimešová and Heyrovský maintain that the actomyosin-bound ATPase can easily be separated from other ATPases by inhibition of the former by Salyrgan.[66] It could be shown that there is a parallelism between the smooth muscle content and actomyosin-bound ATPase in various arteries. For more details of these and related problems see the review of Somlyo and Somlyo.[120]

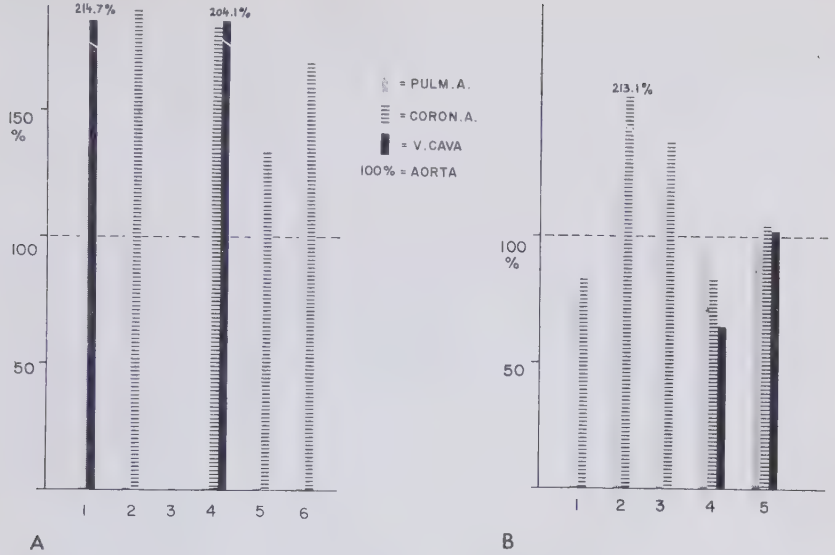

Figure 4. *A*, Differences in enzymes of the tricarboxylic acid cycle (and related enzymes) between the normal human aorta, pulmonary artery, coronary artery and vena cava. For explanation of symbols see Figure 2. *B*, Differences in enzymes of the pentose phosphate pathway between the normal human aorta, pulmonary artery, coronary artery, and vena cava. For explanation of symbols see Figure 3. (Constructed according to data from Kirk, J. E.: Enzymes of the Arterial Wall. New York, Academic Press, 1969.)

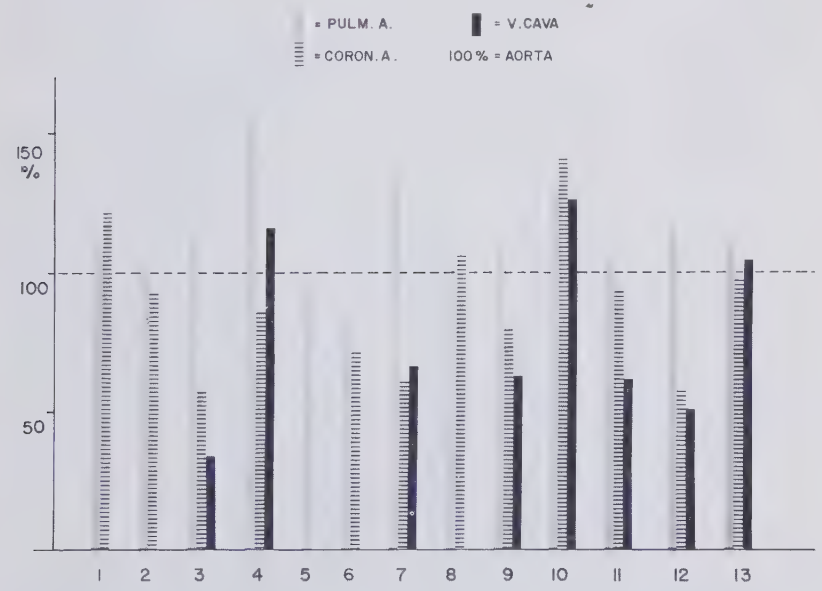

Figure 5. Differences between the normal human aorta, pulmonary artery, coronary artery and vena cava in enzymes of glycolysis and the glycolytic pathway. For explanation of symbols see Figure 1. (Constructed according to data from Kirk, J. E.: Enzymes of the Arterial Wall. New York, Academic Press, 1969.)

Returning to our own results as described above, it is important to emphasize that in most cases they were obtained from necropsied vessels of older persons where it is often very difficult, if not impossible, to decide whether "normal" vascular segments are really free of discrete atherosclerotic lesions. Studies of the enzymatic pattern in arteries of children, young subjects and many young mammals and birds yielded very instructive data. They are summarized in Table 1 together with the more important results obtained with arteries of older subjects.

It can be seen that in contrast to data obtained in studies of vessels of older persons, comparison of abdominal and ascending aortas of children reveals a ratio of Krebs cycle enzyme activities that is quite the reverse of that seen in older individuals and the activity of phosphomonoesterases is approximately identical in both segments. The same could be found in the aortas of young ducks, calves, and monkeys, whereas in chickens the ratio of phosphomonoesterases is also reversed (Fig. 6 and Table 1). On the basis of these findings in human and animal vessels one can infer that the age-dependent changes in the enzymatic pattern are part of a general phenomenon, which may be an essential factor in determining the localization as well as the progression of atherosclerosis.

At this point it is important to mention that simultaneous histochemical studies have revealed that enzyme activity in the smooth muscle cells is clearly the decisive factor that determines the overall activity in the arteries.[88, 89, 136, 148] All of the age-linked changes in susceptible arterial segments seem to depend on the quantity and conditions of the vascular smooth muscle cells. Figure 7 is an illustrative example of staining for malate dehydrogenase in the arteries of a child. The activity is located

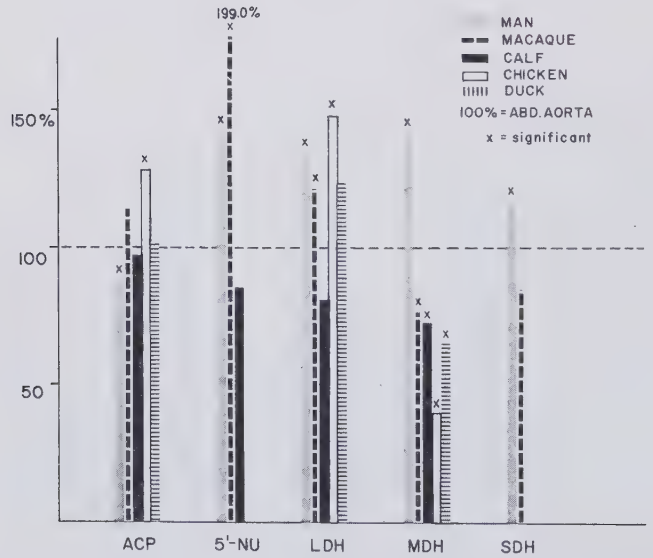

Figure 6. Enzyme activities in ascending aortas of man and some animals as compared with activities in the abdominal aortas. (Constructed according to data from Zemplényi, T.: Enzyme Biochemistry of the Arterial Wall as Related to Atherosclerosis. London, Lloyd-Luke, 1968.)

Table 1. *Comparison of Some Enzyme Patterns in Human and Animal Arteries and Arterial Segments**

	TRICARBOXYLIC ACID CYCLE ENZYMES	ACID AND/OR ALKALINE PHOSPHATASE
Abdominal as compared with ascending aorta in 30-day-old chickens	↗	↘
Abdominal as compared with ascending aorta in 50 to 60-day-old ducks	↗	→
Abdominal as compared with ascending aorta in 30-day-old calves	↗	→
Abdominal as compared with ascending aorta in young rhesus macaques	↗	→
Abdominal as compared with ascending aorta in young children	↗	→
Abdominal as compared with ascending aorta in older humans	↘	↗
Femoral as compared with branchial artery in older humans	↘	↗
Thoracic aorta as compared with pulmonary artery in older humans	↘	↗

**From* Zemplényi, T., Urbanová, D., and Mrhová, O.: *In* Laszt, L., ed.: International Symposium of Biochemistry of the Vascular Wall. New York, Karger, 1969, p. 162, by permission.

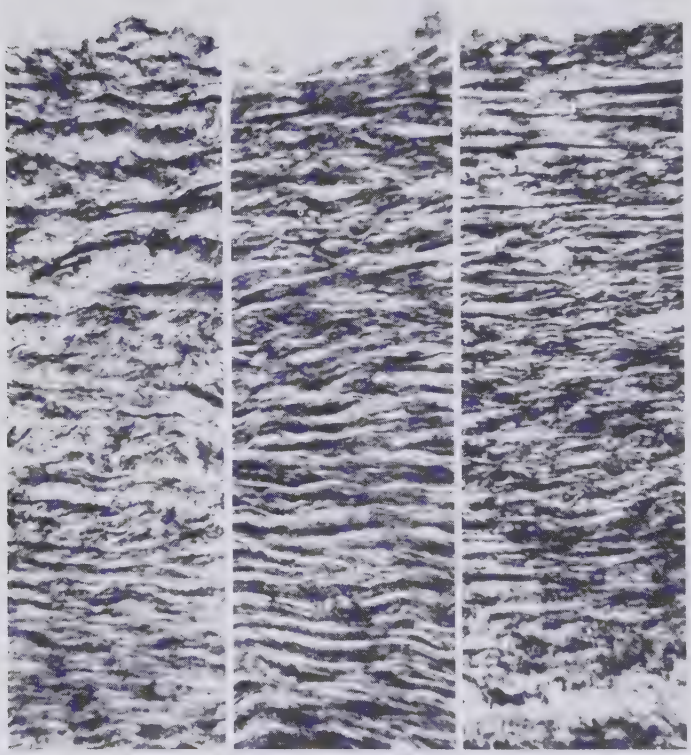

Figure 7. Malate dehydrogenase in the ascending aorta (left), abdominal aorta (middle), and pulmonary artery (right) of a child. × 350. (*From* Zemplényi, T., Urbanová, D., and Mrhová, O., *in* International Symposium on Biochemistry of the Vascular Wall. Basel and New York, Karger, 1969, p. 162, with permission.)

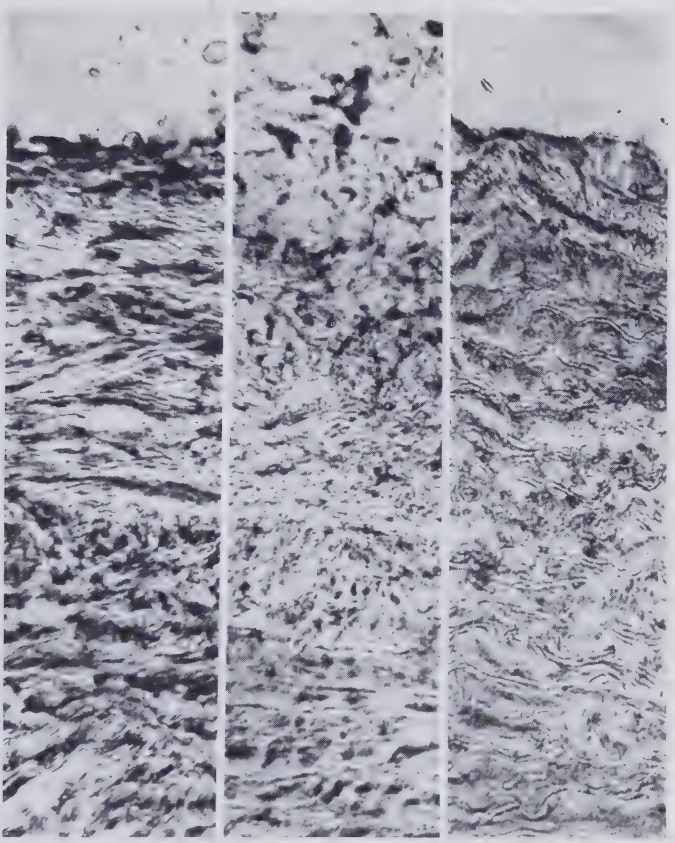

Figure 8. Malate dehydrogenase in the ascending aorta (left), abdominal aorta (middle) and pulmonary artery (right) of a 40-year-old man. × 350. (*From* Zemplényi, T., Urbanová, D., and Mrhová, O., *in* International Symposium of Biochemistry of the Vascular Wall. Basel and New York, Karger, 1969, p. 162.)

mainly in the muscle cells of the media but also in the endothelium and the *vasa vasorum*. The abdominal aorta shows more intense overall staining than the ascending aorta. However, as shown in Figure 8, in the aorta of a 40 year old man only a weak staining reaction can be observed in the abdominal aorta whereas the staining reactions (enzyme activities) in the ascending aorta and pulmonary artery are unaffected.

THE ROLE OF VASCULAR INJURY

The question arises as to what are the factors that induce the age-dependent enzymatic alterations in the less durable arteries, especially in their smooth muscle cells? It is widely held by many investigators that the early atherosclerotic lesions in man and animals begin as a reparative response to injury caused perhaps by the wear and tear of daily life. To explore this, several experimental models of vascular injury were

investigated. The models were injury induced by calciferol feeding,[140] injury caused by increased intravascular pressure, and injury induced by allylamine administration.[148, 149] All of these factors are also known to facilitate the development of lesions similar to atherosclerosis in hyperlipidemic animals.

Table 2 summarizes some of the aortic enzyme activity changes resulting from the different vascular injuries. We see that in all four types of experiments acid phosphomonoesterase activity increased whereas nonspecific carboxylic esterase activity decreased. The activity of Krebs cycle enzymes (malate and succinate dehydrogenase) decreased in DOCA + NaCl hypertension, in allylamine intoxication and in the later stages of calciferol injury. Furthermore, they tended to decline in rats with hypertension induced by renal artery clamping. One can also see that the other enzymatic alterations did not reveal such a uniformity. Assuming that vascular injury is a common denominator in all these experiments, it seems reasonable to conclude that increased phosphomonoesterase activity as well as decreased activities of nonspecific carboxylic esterase and of Krebs cycle dehydrogenases constitute a common feature of vascular wall injuries.

It has to be mentioned that experimental evidence from other tissues reveals that injury causes a decline in the concentration and activity of many cytoplasmic and mitochondrial enzymes, probably as a result of leakage accompanying permeability changes and damage to intracellular structures. On the other hand, the increased intracellular level and activity of other enzymes probably arises from damage and disruption of lysosomes.[24, 94] It is very likely that the same mechanism is responsible

Table 2. *Some Enzyme Patterns in Different Types of Experimental Vascular Injury*†

VASCULAR INJURY BY	ACID PHOSPHATASE	5′-NUCLEOTIDASE	ATPASE	CARB. ESTERASE	TCA CYCLE ENZYMES
Allylamine intoxication	↗	→	↘	↘ **	↘
Excess vitamin D feeding	↗	⇢	⇢	↘	↘ ***
DOCA + NaCl hypertension	↗	→	↘	↘	↘
Renovascular hypertension	↗	↗	→	↘	⇢ *

*Strong tendency.

**So far studied only histochemically.

***Histochemically early decline, biochemically only in more advanced stages.

†*From* Zemplényi, T., Urbanová, D., and Mrhová, O.: *In* Laszt, L., ed.: International Symposium of Biochemistry of the Vascular Wall. New York, Karger, 1969, p. 162, by permission.

for the enzyme activity alterations observed in the arteries of animals subjected to selective vascular injury.

Returning to the arterial wall, one important fact emerges from the studies so far quoted: The enzymatic changes (in particular decrease in activity of Krebs cycle enzymes and increase of phosphomonoesterase activities) which occur in experimental vascular injuries are the same as those which develop in susceptible human arterial segments (and also in experimental atherosclerosis). Such data appear to justify an important conclusion, namely that the vascular segments which are more susceptible to atherosclerosis are also those that are preferentially exposed to damaging agents.

We cannot analyze in the present review all of the physiologic and pathologic factors that may damage the arterial wall and thus contribute to the pathogenesis of atherosclerosis. There can be, for example, little doubt that in this regard hemodynamic and hemorrheologic factors such as lateral pressure, suction pressure, shearing strain, turbulence, and similar parameters play an essential role. In addition, arterial hypoxia appears to be another factor contributing to vascular damage. Many authors maintain that because of the anatomy of the arterial wall, in particular that of the aorta, the mid-zone layers of the arterial tunica media become poorly supplied, especially as a consequence of diffuse thickening of the intima.[4] Histochemical studies[3] and biochemical work[136, 147] have demonstrated that in contrast to other enzymes, total lactate dehydrogenase activity is highest in the mid-zone of the tunica media. A study of isoenzymes of lactate dehydrogenase in multiple consecutive layers of human aortas[136, 147] indicated that an adaptation to hypoxic conditions in the middle zones of the human aorta may be brought about by increased activity

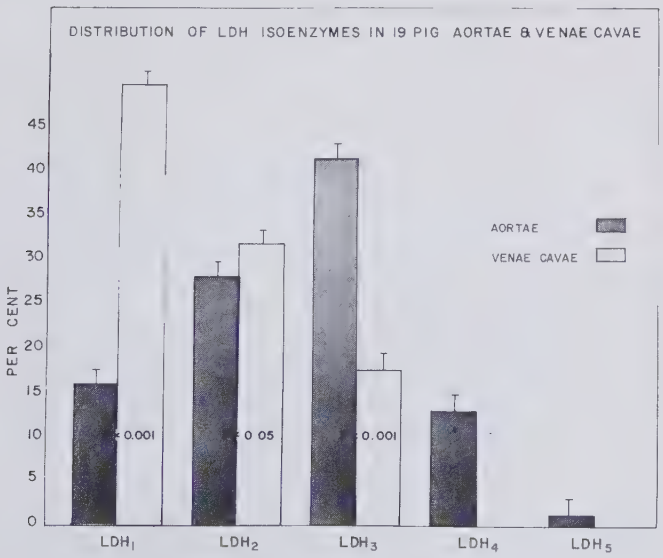

Figure 9. Differences in lactate dehydrogenase isoenzyme activities in pig aorta and vena cava, determined by cellulose acetate electrophoresis.

of the anaerobic (muscle) forms of LDH isoenzymes, proportional to the increased total LDH activity. Furthermore, in human atherosclerotic arteries Lojda and Frič[88] demonstrated a high activity of the slow-moving (anaerobic) lactate dehydrogenase fractions, whereas the activity of the fast-moving (aerobic) fractions are negligibly low. However, in intact arteries of children, the activities of aerobic fractions prevailed.

In this regard comparative investigations of arterial and venous tissue yielded useful results.[150] As shown in Figure 6 there is an unequivocal predominance of LDH_1 (the main aerobic fraction) and a lack of LDH_4 and LDH_5 (anaerobic fractions) in the pig vena cava as compared with the aorta. On the other hand, more than 40 per cent of aortic LDH activity is confined to LDH_3 and only 15.6 per cent to LDH_1. In dog vessels a similar pattern could be detected. According to the current theory,[20] the slow moving cathodic LDH fractions are the principal isoenzymes in anaerobically metabolizing tissues while the fast-moving fractions are the most abundant isoenzymes in the heart and other tissues where a steady supply of energy is maintained by complete oxidation in the presence of oxygen. Although some investigators have expressed some doubt as to the general validity of this hypothesis, it appears to be the prevalent consensus that LDH isoenzyme patterns reflect long-term metabolic conditions of oxygen availability.

In view of the above findings one could assume that the difference in such features between the arterial and venous tissue contributes to the difference in the susceptibility of these vessels to atherosclerotic lesions. In fact, recent evidence implicates hypoxic or anoxic damage of the arterial wall in the pathogenesis of atherosclerosis[65, 112] and the above findings are in agreement. It is interesting that in the miniature swine subjected to high altitude hypoxia, there was also an increase in aortic LDH and a decrease in succinate dehydrogenase activity.[31] In rats fed a hypercholesterol diet a decrease of aerobic LDH fractions in the aorta could be observed.[117]

The data so far mentioned seem to incriminate mainly age-dependent vascular injury as a cause of decreased durability of some parts of the arterial tree. However, this cannot be the whole story as it was repeatedly demonstrated, for example by Haimovici et al.,[40-42] that canine arterial homografts, whether implanted into sites of maximum or minimum involvement, retain their original durability or susceptibility to atherosclerosis. Such findings suggest that susceptibility or durability is an inherent biologic local property of vascular tissue. It is, however, equally reasonable to expect that hemodynamic and hemorrheologic factors, the most probable damaging factors of daily wear-and-tear, have to exert their action for a long time before they prepare in the artery a suitable "terrain" for the development of atherosclerosis. Relatively short-term experiments cannot definitely answer this essential question of atherogenesis.

ENZYMES OF CONNECTIVE TISSUE METABOLISM

Returning now to the problems related to hypoxia, it appears to be well established that local hypoxia is a stimulus for the activation of

fibrogenic cell function, especially for the production of mucopolysaccharides and collagen.[14] One could therefore speculate that the stimulus for initial alterations in arterial connective tissue metabolism is also local hypoxia. In fact, Helin and co-workers observed an increase of aortic mucopolysaccharide and collagen in rabbits exposed to systemic hypoxia.[52, 53]

Until now, 6 enzymes of mucopolysaccharide breakdown have been identified and thoroughly studied in the vascular wall.[12, 49, 50, 51, 61, 93, 98, 106]

The sites of action of these enzymes on chondroitin-4-sulfate-protein are shown in Figure 10. In the first catabolic phase hyaluronidase and chondroitinsulfatase catalyze depolymerization and removal of ester sulfate. The resulting sulfate-free oligosaccharides are afterwards degraded by the alternating action of beta-glucuronidase and beta-acetylglucosaminidase. The protein component is degraded by cathepsin D and acid carboxypeptidase.[12, 51] The breakdown is probably completed by such hydrolases as leucine aminopeptidase. The result is degradation into N-acetylagalactosamine, glucuronic acid, inorganic sulfate, oligosaccharides, glycopeptides, peptides, and amino acids.[51]

The activity of chondroitinsulfatase is the lowest of the 6 enzymes and the reaction catalyzed by it could represent a rate-limiting step in the process of arterial mucopolysaccharide breakdown.[51] Hayase et al.[49] observed an identical activity of beta-acetylglucosaminidase in human, chicken, and rat aortas but a much lower activity in rabbit, pig, and dog aortas. In bovine aortas, where the most complete studies were carried out by Buddecke and co-workers, only cathepsin D and acid carboxypeptidase activity revealed an increase with age whereas hyaluronidase ac-

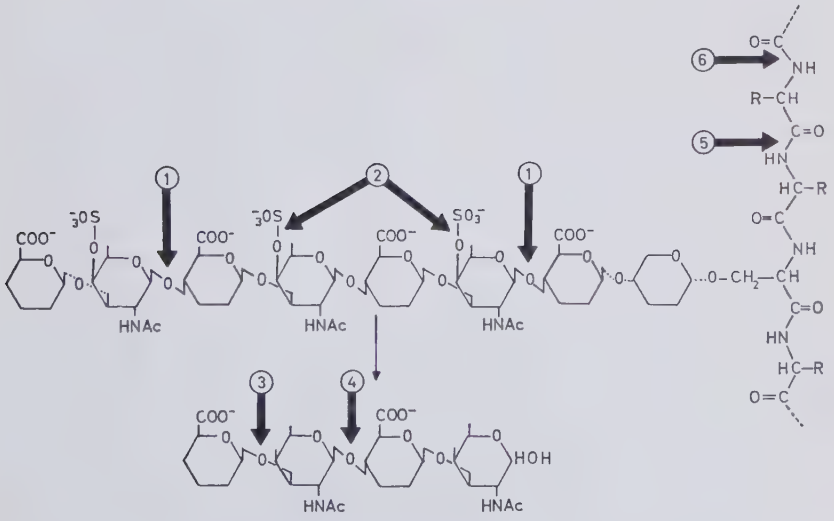

Figure 10. Enzymes of chondroitin-4-sulfate-protein catabolism. 1, Hyaluronate glycanohydrolase. 2, Chondroitinsulfate sulfohydrolase. 3, β-Glucuronidase. 4, β-N-Acetylglucosaminidase. 5, Cathepsin D. 6, Acid carboxypeptidase. (*From* Buddecke, E., and Kresse, H.: Angiologica, 6:89, 1969, by permission.)

tivity decreased and the activities of beta-acetylglucosaminidase and beta-glucuronidase remained unchanged. All these activities were calculated on the DNA content basis of the arteries. In human arteries the data dealing with correlation between age and enzyme activity are conflicting.[12, 106]

Much less controversy exists as far as the activities in atherosclerotic vessels are concerned. In experimental atherosclerosis in rabbits[98] as well as in spontaneous atherosclerosis in rats[129] there is an unequivocal increase in arterial beta-glucuronidase activity. In human atherosclerosis an increased activity of beta-glucuronidase, beta-acetylglucosaminidase, cathepsin D, and acid carboxypeptidase could be detected in several laboratories.[11, 12, 25, 61, 93, 94] It is interesting that normal segments of atherosclerosis-resistant vessels, such as the internal mammary artery, reveal a higher beta-glucuronidase activity than the more susceptible abdominal aorta or coronary artery.[93] The same perhaps applies to the pulmonary artery, but the beta-acetylglucosaminidase activity in the pulmonary artery and coronary artery is the same as in the aorta.[61]

To the present reviewer's knowledge, so far only one enzyme involved in mucopolysaccharide synthesis has been studied in arterial tissue. The activity of hexosephosphate aminotransferase ("hexosamine-synthesizing enzyme") is definitely lower in the pulmonary artery than in the aorta and there is a trend toward decreased activity in the atherosclerotic coronary artery.[46]

We can conclude on the basis of the data concerned with enzymes of mucopolysaccharide metabolism that there is without a doubt an increased catabolic activity of mucopolysaccharides in the atherosclerotic vessel, leading to depolymerization and eventually total degradation of this essential component of the artery. Does this contribute to the increased affinity to lipoproteins as mentioned in the introduction?

So far very little is known about enzymes of collagen and elastin metabolism in the arterial wall. The activity of protocollagen proline hydroxylase, the enzyme considered to be a controlling factor in collagen synthesis, increases in rabbit aortas as early as 4 days after production of atherosclerosis-like plaques by simultaneous injection of epinephrine and thyroxine.[32, 33] Further studies of the enzyme in relation to atherogenesis are highly desirable. Changes of its activity again focus attention to hypoxia as a pathogenetic factor, as recent studies in other organs indicate that low oxygen pressure may influence the activity of the enzyme.[15]

The last enzyme to be mentioned in relation to arterial connective tissue is elastase, which is interesting not only as a peptidase acting on elastin but also because there is some evidence to indicate a possible relationship between enzymes of the elastase complex ("elastomucase") and between lipoprotein lipase.[6, 43, 81, 82] In human aortas Gore and Larkey[37] found only a weak elastase activity, but later Citterio and Cunego,[16] using a more sensitive method, demonstrated a high activity in normal human cerebral arteries and a decline in activity in atherosclerotic vessels. Pretolani[108] was able to detect notable activity but the method used appears to be open to discussion. However, Loeven[83] demonstrated both in calf and cow aortas a small but consistently present amount of elasto-

proteinase and elastomucase. "Elastolipoproteinase" could not be definitely proved.

In view of the recent findings of unequivocal arterial elastase activity, one cannot deny the attractiveness of the possible pathogenetic significance of elastase as postulated by some authors, namely, that the elastoproteinase fraction of the elastase complex primarily damages arterial elastic tissue, whereas the elastomucase (or elastolipoproteinase?) fraction prevents secondary lipid infiltration.[44, 45] It is interesting in this connection, that in the blood platelets there is also a protease attacking elastin and the enzyme is liberated from platelets during their aggregation on collagen or by ADP.[110] Injury caused by enzymes released from platelets is implicated[99] as a factor contributing to the accumulation of lipoproteins in the arterial wall.

ENZYMES RELATED TO TRIGLYCERIDE AND PHOSPHOLIPID METABOLISM

Until now no mention has been made of enzymes immediately connected with lipid metabolism, although lipid accumulation is one of the hallmarks of the atherosclerotic lesion. In comparison with other enzymes information on this subject is much poorer.

3-Hydroxyacyl-CoA dehydrogenase, catalyzing an important step in the synthesis, as well as breakdown of fatty acids, has high activity in human arteries and has a tendency to decrease with age.[114] The activity in the vena cava is only about one third of that in the arteries. In atherosclerotic aortas the activity significantly decreases. Similarly, the activity of carnitine transferase, an enzyme enabling the transfer of fatty acids across the mitochondrial membrane and their oxidation by mitochondria, is very significantly lower in atherosclerotic human aortas and coronary arteries. Interestingly enough, the carnitine content of the atherosclerotic aorta is higher than that of the normal aorta, but the ratio is reversed in the coronary artery.[62] It is clear that much more data on enzymes of fatty acid metabolism are needed before any definite conclusions can be made on this important facet of lipid metabolism in the arterial wall.

A clearer picture seems to emerge from studies connected with other aspects of arterial lipid metabolism.

In 1955 Korn observed lipoprotein lipase activity in ammonia extracts of acetone-powders from a few rat aortas, using chylomicrons as substrate.[67] Independently of these observations, we subjected the question of arterial lipolytic activity to detailed investigation in our laboratory in Prague. It could be demonstrated, using lipemic serum, rat chyle or later "activated" lipid emulsions as substrates and measuring the amount of free fatty acids liberated, that the degree of lipolytic activity of the aorta was very significantly higher in the relatively atherosclerosis-resistant rat than in the rabbit, guinea pig, or chicken.[137, 143] The lipolytic activity of the aorta significantly decreases in adult rats with increasing age[139] but increases in experimental rabbit atherosclerosis.[138] The lipolytic activity in aortas of rats treated with high doses of calciferol was found significantly decreased.[39]

Other authors, using basically the same or slightly modified techniques, confirmed and extended the above findings.[5, 74, 75, 79, 92] Experiments using different substrates and inhibitors indicated that other lipolytic enzymes besides lipoprotein lipase were also involved in arterial lipolysis.[38, 48, 134, 152] Human aortic mucopolysaccharide mixtures are claimed to inhibit vascular lipolytic activity.[35]

It was demonstrated that carboxylic (nonspecific) esterase activity usually, but not always, runs parallel with lipase activity, and the detection of the former by histochemical techniques is relatively simple. In experimental atherosclerosis the early plaque constituents exhibit increased staining for nonspecific esterase with all histochemical methods used for this enzyme.[86, 89] By a combination of biochemical and histochemical techniques it could be shown that in animals alloxan diabetes,[76, 79] hypothyroidism,[75] immobilization stress,[80] or prolonged treatment with ACTH[102] induces a decrease in arterial lipolytic activity. In hypertensive animals there appears to be an increase in aortic lipolytic activity,[92] although the esterase activity declines.[148] An increase in aortic lipase activity in atherosclerotic rabbits could be prevented by injection of polyunsaturated lecithin.[105]

In connection with the probable mechanism of increased lipolytic activity in atherosclerotic vessels it is instructive that in animals actinomycin D treatment prevents the increase of esterase activity in connective tissue cells.[78] By analogy, one can assume that the increased activity in atherosclerotic vessels is an adaptive change based on a substrate-linked induction of lipolytic enzymes.[136]

The presence of lipoprotein lipase-like activity in human arteries was reported by several authors.[5, 48, 61, 77, 104] The activity in the normal thoracic aorta is about 4 times higher than in the abdominal aorta.[104] Kirk[61] found a significantly higher activity in the pulmonary artery and vena cava than in the aorta. With age the activity in normal aortic tissue has a tendency to decrease.[5] In atherosclerotic aortas from younger adults up to the fifth decade, there appears to be a tendency toward decreased activity, not demonstrable, however, in atherosclerotic aortas of older individuals.[61] The carboxylic esterase activity is, according to Kirk's findings,[61] markedly higher in the atherosclerotic aorta and coronary artery segments than in normal portions of the same vessels. Fibrous lesions do not display such a change in activity. This is in agreement with previous histochemical data in human vessels.[136]

It has to be emphasized that not all arterial lipolytic activity is due to the effect of lipoprotein lipase. In very careful studies, Hayase and Miller[48] demonstrated that normal human aortic tissue contains, besides the alkaline lipase (pH optimum 8.8), also an acid lipase (pH optimum 5.4) differing in physicochemical characteristics. The acid lipase is more resistant to substrate inhibition and this observation leads the authors to speculate that the mechanism to dispose of excess triglycerides may have to rely upon the activity of acid lipase.

The normal arterial wall appears to possess the ability to counterbalance an increased influx of not only triglycerides but other lipids as well. In a series of very well documented papers, Stein and co-workers[26–28, 109, 125–127] investigated the presence and characteristics of phospholip-

ases in animal and human arteries. The most interesting results deal with the activity of sphingomyelin cholinephosphohydrolase, the enzyme that splits sphingomyelin into N-acylsphingosine ("ceramide") and phosphorylcholine. It could be shown that the activity of the enzyme, calculated on the DNA content basis, is much higher in the rat than the rabbit aorta, and in animals as well as man the activity unequivocally decreases with age. In contrast, the activity of phosphatide acyl hydrolase, phospholipase, increases with age (up to 5-fold) whether using lecithin or phosphatidyl athanolamine as substrate. The activity of lysophosphatide hydrolase increases as well.

Since the aortic sphingomyelin content increases very definitely with age and atherosclerosis,[10, 119] the above findings appear to throw some new light on the mechanism of arterial phospholipid-content regulation. The preferential accumulation of sphingomyelin with aging (70 per cent of the total phospholipid increment) appears to result from an imbalance in the rate of its influx (synthesis in situ plus entry from the circulation) and the rate of removal (egress and degradation), while the high activity of the other phosphohydrolases prevents a larger accumulation of the other phospholipids with age, and most likely also in atherosclerosis, in spite of the higher synthesis rate. So far no definite data are available on the activity of these phosphohydrolases in human atherosclerosis; however, a good deal of results have been accumulated on the activity of phospholipase A in normal and atherosclerotic animal arteries,[103, 104, 128] and the results indicate that the aortas in rabbits fed an atherogenic diet display a definite increase in phospholipase A activity.

CHOLESTEROL ESTER HYDROLYZING AND SYNTHESIZING ENZYMES

The last enzymes to be considered are connected with hydrolytic cleavage of cholesterol esters and/or with cholesterol esterification. Patelski and co-workers detected by means of fatty acid titration an unequivocal hydrolytic cholesterol esterase activity in pig, rat, and rabbit aortas.[103-105] Feeding of an "atherogenic" diet to rats and rabbits caused a decline in the enzyme activity. Other authors, using labelled cholesterol oleate as substrate, were also able to observe definite cholesterol esterase hydrolytic activity in rabbit,[21] rat, and monkey aortas,[55] as well as chicken aortas.[118] However, no cholesterol esterase synthesizing activity was reported.

The failure to detect synthesizing activity in previous studies seems to be clarified by recent data by Kothari et al.[68] They demonstrated that the physicochemical state of the substrate greatly influences the detectability of synthesizing activity in aortic samples. With micellar substrates hydrolysis was almost exclusively observed, whereas the use of oleic acid and cholesterol, emulsified with sodium taurocholate, enabled the detection of synthesizing and hydrolyzing activity. Both of these activities are again lower in rabbit than in the relatively atherosclerosis-resistant rat aorta. The demonstration of cholesterol ester synthesizing

activity is in agreement with previous evidence showing cholesterol esterification in arterial tissue.[29, 84, 85, 100, 123, 124, 151]

In addition to cholesterol esterase, an alternate way for cholesterol esterification appears to be present in arterial tissue. Abdulla et al.[1, 2] presented evidence that in normal and atherosclerotic human and rabbit aortas, esterification can be carried out by a lecithin:cholesterol fatty acid transferase. The activity tends to rise in aortas of older subjects and is definitely increased in human atherosclerotic lesions and aortas of cholesterol-fed rabbits. So far, however, other investigators are unable to detect the transacylation reaction in the arterial wall.[23, 124] Nevertheless, the transacylation reaction, if present, could represent an interesting link between cholesterol and phospholipid metabolism in the arterial wall. It releases lysophosphatidylcholin (lysolecithin) from lecithin, and in this regard it is interesting that in the atherosclerotic aorta from squirrel monkeys the concentration of the latter compound is claimed to be nearly eight times higher than in comparable control tissue.[107] However, there is also good evidence that lysolecithin is rapidly removed from plasma by arteries, and therefore, it may be a product of the lecithin:cholesterol fatty acid transferase reaction in plasma. The important aspect of arterial lysolecithin accumulation is the fact that the compound is of great importance in aortic phospholipid and perhaps also triglyceride synthesis.[125–127]

SUMMARY AND CONCLUSIONS

Understanding of the pathogenesis of atherosclerosis requires detailed knowledge of the metabolic characteristics of arterial tissue, and in particular of its multifunctional smooth muscle. Study of arterial enzymes is one of the promising approaches to achieving this goal. Blood vessels can no longer be viewed as mere blood pipes, and on *a priori* grounds one can expect that most enzymes characteristic of all living matter will be found in vascular tissue. The evidence so far assembled conclusively shows that the arterial wall contains enzymes that catalyze basic reactions of metabolic "mainstreams." The artery also contains enzymes catalyzing special reactions such as cholesterol ester hydrolyzing and synthesizing enzymes, phospholipases, and lipases, and their study provides valuable data on the possible mechanisms of lipid accumulation in the arterial wall.

Arterial enzyme activities change with age, especially over the age of 40, and some activities manifest clear-cut sex-linked differences and are probably regulated by hormones. The activities of most enzymes show significant alterations in atherosclerotic arteries. However, investigation of advanced lesions does not answer the question whether such activity-changes precede atherosclerosis or result from the development of the disease. This is considered by the present reviewer the crucial problem in the study of the relationship between vascular metabolism and atherosclerosis. The study of very early stages of spontaneous and experimental animal atherosclerosis should add a great deal to our knowledge in this regard. In addition, comparison of enzyme activities between relatively resistant (durable) and susceptible human and animal arteries indicates

that the susceptible vessels exhibit a lower activity of Krebs cycle enzymes and a higher activity of some phosphomonoesterases than the durable arteries or arterial segments. Further evidence indicates that such a pattern of enzyme activities develops during life, probably as a result of the wear-and-tear of the artery at hemodynamically more vulnerable sites.

Several lines of evidence indicate that tissue hypoxia may be an additional factor causing vascular damage. Local hypoxia may also be a stimulus for changes in connective tissue metabolism, and the evidence assembled indicates that the activities of many enzymes involved in connective tissue metabolism, in particular those of mucopolysaccharide metabolism, undergo significant changes in situations connected with the development of atherosclerosis.

In spite of advances in this field, many important problems arise and many questions remain unanswered. For example, in arteries susceptible to atherosclerosis, the activity of Krebs cycle enzymes is low and there is good reason to presume that respiration and oxidative phosphorylation are also impaired in such vessels. This should necessarily result in decreased production of energy-rich phosphate bonds and reduced vascular synthetic activity with reduced output of proteins, including enzymes. However attractive such a hypothesis may be, it has to await confirmation by investigation of the energy metabolism of the arterial wall, which is technically more difficult than in other tissues.

It must also be pointed out that little information is yet available about endocrine or other regulatory mechanisms of vascular metabolism. Without an understanding of these mechanisms we cannot achieve the final aim – prevention and treatment of atherosclerosis by influencing the resistance of the artery against the development and progress of the disease.

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ADDENDUM

The manuscript of this review was finished in November 1971. Since that time, several important studies related to the present topic have been published. It would therefore be useful to call attention to at least a

few of them. Some new aspects of arterial bioenergetics and lipid metabolism have been published by S. Dayton and S. Hashimoto (Atherosclerosis *12*:371, 1970); I. Filipovic and E. Buddecke (Eur. J. Biochem. *20*:587, 1971); E. S. Morrison and co-workers (Circulation *44*:II-7, 1971; Atherosclerosis *16*:157, 1972; Biochem. Med. 7:308, 1973); C. F. Howard (Atherosclerosis *15*:359, 1972); and G. M. Chisolm and co-workers (Atherosclerosis *15*:327, 1972). The data indicate that fatty acids may provide a substrate for oxidative phosphorylation in arterial tissue. They also show that under hypoxic conditions there is an increase of ^{14}C incorporation from labeled glucose into the glycerol moiety of glycerides and into phospholipid glycerophosphate. In normal aortas, oxygen deficiency reportedly stimulates mitochondrial fatty acid synthesis from acetate, but there is no consensus that this also takes place in the atherosclerotic artery.

A considerable amount of work has been devoted to arterial cholesterol esterase activity: V. Felt (Experientia 27:1412, 1971), Kritchevsky (Lipids 7:305, 1972), and H. V. Kothari and co-workers (Biochim. Biophys. Acta *296*:446, 1973). According to J. W. Proudlock and A. J. Day (Biochim. Biophys. Acta *260*:716, 1972), there exist at least two arterial enzyme systems capable of incorporating labeled cholesterol and fatty acids into cholesterol esters. The first has a pH optimum of 5.0 and does not require ATP and coenzyme A for activity. The second enzyme system, with a pH optimum in the region of 7.5, is dependent upon the presence of coenzyme A and ATP and requires thiol reagents for maximal activity. The latter enzyme appears to be similar to that described previously by Felt and Beneš[29] and by St. Clair.[124]

More new details on arterial metabolism have been recently reviewed by the present author in a chapter to be published in *The Handbook of Experimental Pharmacology*, volume "Pharmacology of Hypolipidemic Agents" (New York, Springer-Verlag).

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Carbon Monoxide, Smoking, and Atherosclerosis

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Several thousand papers have appeared during the years on the association between smoking and atherosclerosis. Of course, a full review of these cannot be given here, so the readers are referred to the many excellent reviews which exist concerning the various aspects of the relationship. Some of the more important ones[30, 59, 64] are mentioned in the text.

The present authors have been especially interested in the pathophysiologic mechanisms involved in the development of atherosclerosis in smokers, and have advocated the hypothesis that it is the carbon monoxide and not nicotine in the tobacco smoke, which is responsible for the much greater risk of smokers developing atherosclerosis in comparison to nonsmokers. We should therefore prefer here to deal especially with this hypothesis and its experimental and clinical background, when considering the various aspects – epidemiologic, clinical, pathogenetic – of the association between smoking and atherosclerosis.

SMOKING AND CARDIOVASCULAR DISEASES

Coronary Heart Disease

Numerous epidemiologic studies have been carried out in various countries in order to demonstrate an association between smoking and the development of coronary heart disease. It is beyond the scope of this review to cover all these studies. Excellent reviews are given in the yearly reports to The Surgeon General, "The Health Consequences of Smoking," and in a report (1971) of The Royal College of Physicians in London: "Smoking and Health Now." The epidemiologic studies, retrospective as well as prospective, have given very clear-cut results, showing an enhancement of the frequency of coronary heart disease in smokers in comparison to nonsmokers. This is especially striking when

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considering the risk among cigarette smokers of younger age groups dying from this disease, which is two or three times as great as that of nonsmokers. For Britain it has been calculated that in the absence of cigarette smoking the death rate from this disease between the ages of 35 and 64 might be reduced by 25 per cent in men and 20 per cent in women.[64]

The total number of deaths attributed to coronary heart disease is rising steadily in all developed countries from various causes. The main risk factors are high blood pressure, high serum cholesterol, low physical activity, and cigarette smoking. The effect of smoking is independent of the presence of the other risk factors when they are considered separately, as illustrated in Table 1. Several American studies have demonstrated a dose-related effect of cigarette smoking on the risk of developing coronary heart disease, and autopsy studies have shown that aortic and coronary atherosclerosis were more common and more severe among smokers in comparison to nonsmokers.[30] The incidence of coronary heart disease is higher in inhaling smokers than in noninhaling smokers, and higher in cigarette smokers than in smokers of pipes or cigars, who have a risk not much higher than nonsmokers. Ex-cigarette smokers have a steady decline of risk of coronary heart disease and after 10 years of abstinence the risk is close to that of nonsmokers.[30, 64]

Table 1. *Effect of Cigarette Smoking on Incidence of Coronary Heart Disease in Men with and without Other Risk Factors**

RISK FACTOR	CONTRASTING GROUPS	RATIO OF CHD INCIDENCE COMPARED WITH NON-SMOKERS IN LOWER RISK GROUP	
		Non-cigarette smokers	Cigarette smokers
Blood pressure (systolic)	Under 130	1.0	2.1
	130 or more	1.8	3.8 (2.1)
Blood cholesterol	Low	1.0	1.8
	High	2.0	4.5 (2.3)
Physical activity	Most active	1.0	2.6
	Least active	2.4	3.4 (1.4)
Social mobility	Stable	1.0	1.5
	Mobile	2.3	3.2 (1.4)
Behaviour type	Type B	1.0	2.0
	Type A	2.5	4.4 (1.8)

*This table, published in "Smoking and Health Now" (1971), is derived from American studies, reviewed in The Health Consequences of Smoking (1967).[59] It gives the age-standardized incidence of coronary heart disease in men, taking the incidence of non-cigarette smokers in the lower risk group as 1.0. The figures in parentheses give the increased risk of cigarette smokers compared with non-cigarette smokers in the higher risk group. Published with the permission of The Royal College of Physicians (London).

The association between coronary heart disease and cigarette smoking seems to be more pronounced in the United States, Canada, and the United Kingdom than in many other countries. In a 1964 study[2] a mortality rate for coronary heart disease was found to be 51 for Japan in comparison to 364 in the United States, in spite of the fact that the Japanese were the heaviest smokers as found in a study of similar groups in 7 countries including the United States.[38] This indicates that the effects of smoking on the development of coronary heart disease might be explained as an enhancement of the effects of already existing risk factors.

Angina Pectoris

Angina pectoris occurs more frequently in smokers than in nonsmokers.[64] The pains are usually associated with reduced oxygen supply to the myocardium, most frequently caused by obliterations in the coronary arteries. It should be emphasized that myocardial ischemia is greatly enhanced by carbon monoxide exposure, since the affinity of oxygen to myoglobin is two to three times higher than to hemoglobin. The occurrence of even low concentrations of carboxyhemoglobin may therefore have a serious effect on the oxygen transport system in the myocardium of normal hearts, and will aggravate the effect of a decreased blood flow caused by coronary obliterations.

Peripheral Atherosclerosis

Several studies have shown that cigarette smoking is one of the risk factors in the development of peripheral obliterating arterial diseases.[30] This is especially true for thromboangiitis obliterans (Buerger's disease). It has been much discussed whether this disease is a clinical entity separate from peripheral atherosclerosis, a view which some authors support,[1, 8] while others oppose.[21, 69] The effects of cigarette smoking are especially convincing concerning the progression of arterial insufficiency, since most authors here agree that continuation of smoking gives a bad prognosis, while cessation of smoking stops progression.

Cerebrovascular Disease

American epidemiologic studies on cerebrovascular disease indicate that cigarette smoking is associated with increased mortality at all ages up to 75.[30, 64] The association is less pronounced than for coronary heart disease and cigarette smoking.

PHYSIOLOGIC AND PATHOLOGIC EFFECTS OF NICOTINE

Smoke from a cigarette contains from 0.5 to 3 mg. of nicotine, depending on the different brands. When the smoke is inhaled practically all the nicotine is absorbed, and the plasma nicotine levels may increase up to 40 to 50 ng. per ml. of plasma.[34] The rate of elimination seems, however, to be high enough to prevent appreciable accumulation from day to day. Nicotine from the acid cigarette smoke is absorbed mainly in the lungs, while nicotine in the alkaline smoke from pipes and cigars, be-

cause of the higher concentration of its un-ionized form, is absorbed also through the mucous membrane of the mouth.[3] Cigarette smokers absorb on an average three times as much nicotine as cigar or pipe smokers.[36]

Cardiovascular Effects of Nicotine

For many years nicotine and related compounds have been considered as the cause of the harmful effects of tobacco smoking, owing to the various acute cardiovascular responses to parenteral administration of nicotine or to the inhalation of tobacco smoke. Nicotine is a stimulator of both sympathetic and parasympathetic ganglia, and nicotine inhaled in cigarette smoke increases the arterial epinephrine concentration in man. Catecholamines are also liberated from isolated hearts by nicotine administration.[30, 59, 64]

The cardiac effects of nicotine administration in normal subjects include increases in heart rate, cardiac output, blood pressure, and coronary blood flow. Nicotine may further predispose to the initiation of arrhythmia, particularly when the myocardium is damaged.[11] The increase in coronary blood flow is proportional to the nicotine-induced increase in myocardial oxygen consumption, and probably secondary to that.[39]

In animals with damaged myocardium and in humans with coronary heart disease the response to nicotine administration or cigarette smoking may not lead to an increase in oxygen consumption or coronary blood flow,[30, 56] indicating that patients with coronary heart disease may not be able to respond to the stimulus of cigarette smoke in the same way as normal individuals,[22] and the cardiac output may fall.[55] Furthermore, nicotine administration leads to a decrease in ventricular fibrillation threshold in animals,[13] to increased arrhythmia in animals with damaged myocardium,[11] and to decreased conduction velocity and increased automaticity of the Purkinje fibers system.[23] It should be noted that, in general, the pulse rate is increased only to a very moderate degree in smokers in comparison to nonsmokers, at an average of between one and two beats,[24] and the average arterial blood pressure is also approximately the same in the two groups.[59]

Nicotine administration and cigarette smoking cause a constriction of the peripheral blood vessels, leading to a temporary fall of skin temperature.[30, 59, 64]

Effects of Nicotine on Lipid Metabolism

Nicotine administration and cigarette smoking lead to an increase in free fatty acids in serum, as first observed by Kershbaum et al.[35] The increase is mediated by catecholamine release.[37] There is no change in serum concentrations of triglycerides, cholesterol, and phospholipids.[30, 60] Rabbits given 1.14 mg. of nicotine per kg. of body weight twice daily for 20 months did not show changes of lipids in heart and aorta. In liver the concentration of neutral fat decreased, and the concentration of free fatty acids increased; an increase in lipoprotein lipase activity in heart and aorta was also found.[60] Otherwise no reports have appeared on any significant influence of nicotine on lipid metabolism.

Nicotine and Experimental Atherosclerosis

Several studies have dealt with the effect of nicotine administration upon the atherosclerotic changes in animals.[30] The daily dosage of nicotine has in general been several times higher per kg. of body weight than the daily amount of nicotine adsorbed by heavy smokers. The main results are that, when administered alone, nicotine has no atherogenic effect. In combination with the administration of cholesterol, the atherosclerotic lesions are found by most authors to be enhanced, but not by all.[30] Necrosis and calcifications of the medial layers of aorta were often seen,[30,60] and this might be explained by an effect of catecholamines, since the administration of those to animals has a similar effect.[49] Peroral nicotine administration has no synergistic effect on carbon monoxide-enhanced atherosclerosis in cholesterol-fed rabbits.[6]

Nicotine and Blood Clotting

The effect, if any, of smoking on blood coagulation and function of platelets is probably related to an action of nicotine, since carbon monoxide exposure does not seem to have any effect.[48] Reviews on the effect of smoking have been given in 1968 in The Health Consequence of Smoking[29] and by Murphy.[59] The main conclusions are that smoking probably does not influence fibrinolysis and coagulation, but it might affect the platelets by increasing the aggregation and the stickiness to a certain extent. Most of the investigations have dealt with platelet reactivity in vitro using ADP induction.[28,59] The present authors are of the opinion that the formation of thrombi does not initiate the atherosclerotic process, but may lead to occlusion of atherosclerotic arteries as a result of platelet aggregation at injured parts of the endothelium. It has been found by autopsy studies that the frequency of thrombi increases with increasing survival time after acute attacks, suggesting that the thrombi found at autopsy may be the result rather than the cause of certain cases of myocardial infarction.[65]

PHYSIOLOGICAL AND PATHOLOGICAL EFFECTS OF MODERATELY INCREASED CARBOXYHEMOGLOBIN LEVELS

Carbon monoxide is produced from technological and natural sources in an estimated global amount of at least 250 million tons per year. Fuel combustion by motor vehicles is the major source. The gas is released to the air, and since the background level does not increase, it is assumed that oxidation to carbon dioxide takes place in the upper atmosphere.

Only a negligible amount of this huge production is taken up by man. When disregarding the relatively rare cases of real carbon monoxide poisoning, the most frequent source of elevated carboxyhemoglobin (COHb) levels is the carbon monoxide in inhaled tobacco smoke. Air pollution in cities with carbon monoxide leads to only very moderately increased COHb levels in nonsmokers (Table 2).

Cigarette smoke contains from 3 to 6 per cent carbon monoxide,

Table 2. *COHb Levels (Per Cent) in Various Groups*

0.5–1.0	Normal individuals
1.0–3.0	Hemolytic conditions
1.4–3.0	Nonsmoking taxi drivers in London
1–20	Smokers
20–80	Carbon monoxide poisoning

about 20 to 30 ml. per cigarette, depending on the temperature of combustion. Smoke from pipes and cigars, burning at a lower temperature than cigarettes, has concentrations of carbon monoxide that are 2 to 3 times higher.[31, 59]

The uptake of carbon monoxide by smokers takes place in the lungs, and thus depends on the degree of inhalation. Heavy smokers show the highest COHb levels, and the highest levels of all (15 to 20 per cent COHb) have been found in inhaling cigar smokers.[40]

The elimination of carbon monoxide takes place at a rate of approximately 15 per cent an hour at rest, which means that a COHb level of 20 per cent will decrease to about 17 per cent in 1 hour. The elimination depends on the carbon monoxide pressure gradient between blood and alveolar air and on the ventilation.[4]

COHb concentrations can be measured in various ways. The present authors have earlier used the method described by Hellung-Larsen,[32] having a precision of ± 1 per cent, but have changed to the more precise method of Commons and Lawther,[20] the precision being about ± 0.3 per cent. A modification is described by Buchwald.[17]

Impairment of Oxygen Transport by Carbon Monoxide

The toxic effect of carbon monoxide on the animal organism has probably been known by man since the discovery of fire, and we know it has been recognized as a dangerous poison in ancient times. It was Claude Bernard who first studied its mode of action, and he showed that blood treated with carbon monoxide was unable to bind oxygen, but it is J. S. Haldane who is considered as the real pioneering investigator of the physiology and toxicology of carbon monoxide. Together with some of his co-workers he performed the now classical studies of the effects of carbon monoxide exposure on man. His first paper appeared in 1895.[26] Haldane considered, as a result of his investigations, that the only toxic effect of carbon monoxide was its ability to bind to hemoglobin at a much higher degree than oxygen, thus displacing oxygen in oxyhemoglobin and depriving blood of its oxygen transport ability. As long as this transport function was not seriously impaired, carbon monoxide was regarded as relatively harmless. This was supported by the findings of many physiologists, showing that concentrations of up to 20 per cent of COHb had little or no effect on usual measured physiologic parameters, such as heart rate, cardiac output, respiration, blood pressure, etc., at rest. This is just the opposite effect to that observed for hypoxia. While the venous and tissue oxygen tensions in moderate hypoxia are quite normal, however, this is not the case after exposure to moderate levels of carbon monox-

ide, as was first shown by Campbell in England in 1929.[18] This effect is due to the low degree of cardiorespiratory compensating adjustment and to the displacement of the oxyhemoglobin dissociation curve to the left (Fig. 1). This displacement was first investigated by Haldane[25] in 1912, and later in more detail by Roughton and Darling (1944)[57] and by others, but has never received any physiologic interest, at least until recent years.

The discovery by Sjöstrand[63] in 1951 of the continuous formation of carbon monoxide in the human body by the catabolism of hemoglobin and other heme pigments, explaining the normal carboxyhemoglobin concentration of about 0.5 per cent, added to the conception of carbon monoxide as a relatively harmless gas as long as it did not interfere seriously with the oxygen transport of blood, i.e., as long as the COHb concentrations are below about 20 per cent.

Carbon monoxide has an affinity for hemoglobin about 250 times higher than the affinity of oxygen, thus causing high COHb concentrations at low carbon monoxide levels in ambient air. So, at equilibrium, 200 ppm leads to a COHb level of about 20 per cent. Ten to 15 per cent of the total body carbon monoxide is located extravascularly, being bound to myoglobin and various other heme-containing proteins. It should be noted that the affinity of those proteins to carbon monoxide in general is higher than the affinity of carbon monoxide to hemoglobin. This refers especially to cytochrome P_{450} and to myoglobin. It has been shown that carboxymyoglobin concentrations are approximately 2 to 3 times higher than the corresponding COHb concentrations.[19] It should here be considered that in tissues such as myocardium with low oxygen tensions, there will be a relatively higher binding of carbon monoxide than in tissues

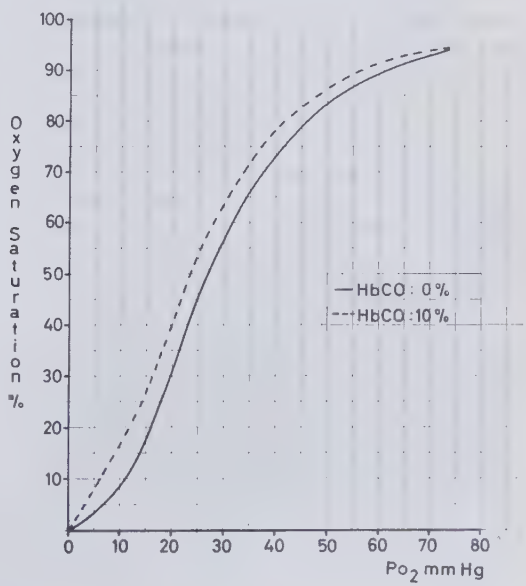

Figure 1. The oxyhemoglobin dissociation curve (pH 7.40, temperature 37° C) at 0 and 10 per cent COHb.

with higher oxygen tensions, dependent on the relation between P_{CO} and P_{O_2} in the various tissues. Thus, the effect of moderate carbon monoxide exposure on the bioavailability of oxygen in tissues is due not only to a lowering of the oxygen content of arterial blood, a lowering of tissue oxygen tensions because of a low degree of cardiovascular adjustment, and a displacement of the oxyhemoglobin dissociation curve to the left, but also to an increased binding of carbon monoxide to heme pigments other than hemoglobin, leading to a still more pronounced impairment of the function of those. This does not necessarily imply a measurable reduction of total oxygen uptake, but may, of course, have serious effects on various intermediary metabolic processes.

Cerebral, Cardiac, and Fetal Effects of Moderately Elevated Carboxyhemoglobin Concentrations

During the last 10 to 20 years the interest in the biologic effects of moderate exposure to carbon monoxide has increased considerably, mainly because of the concern about the risks of the growing air pollution and to the findings of often quite high COHb levels in smokers. The proceedings of two conferences[14, 47] dealing with the effects have been published in 1970 and 1972.

It has been found that the *central nervous system* is influenced, as first shown in the forties by McFarland and his associates,[50] who demonstrated impaired discrimination of small differences in light intensity at 2 and 4 per cent COHb. Also various performances in tests such as the estimation of time intervals without having a clock and the duration of auditory signals are found to be decreased by some investigators at COHb levels of about 5 per cent.[12] Other performance tests may also be discriminated by moderate COHb elevations as described in detail elsewhere.[14, 47]

The *myocardium* can be supposed to be affected by small COHb concentrations, since the utilization of available oxygen is very high at rest. By studying rabbits having COHb concentrations of about 16 to 18 per cent maintained continuously for 2 weeks, severe ultrastructural changes were found.[44] The most impressive findings were focal areas of partial or total necrosis of the myofibrils (Fig. 2) and degenerative changes of the mitochondria. In other areas myelin bodies (Fig. 3) or disintegrations and loss of pattern of the myofibrils were seen (Fig. 4). Characteristic pathologic changes in the mitochondria were swelling, cristolysis, and loss of the limiting membrane (Fig. 5), of fusing of mitochondria into "giant" mitochondria. Other changes in myocardium of carbon monoxide-exposed animals included a large extracellular and intracellular edema, separations of the intercalated discs (Fig. 6), and an increase in the number of lipid droplets, ribosomes, and lipofuscin granules. Reparative fibrotic changes were also noted (Fig. 7). The small coronary arteries exhibited edematous areas with "blister" formation and degenerative changes of the myocytes similar to those seen in elastic arteries (Figs. 10 through 14). Stasis and occasional small perivascular hemorrhages were typical findings in the veins, while the endothelium of the capillaries was occasionally edematous. Preliminary studies indicate that the threshold limit for the harmful effect of carbon monoxide on myocardium is between 100 and 180 ppm after a 4 hour exposure period.

(*Text continued on page 337.*)

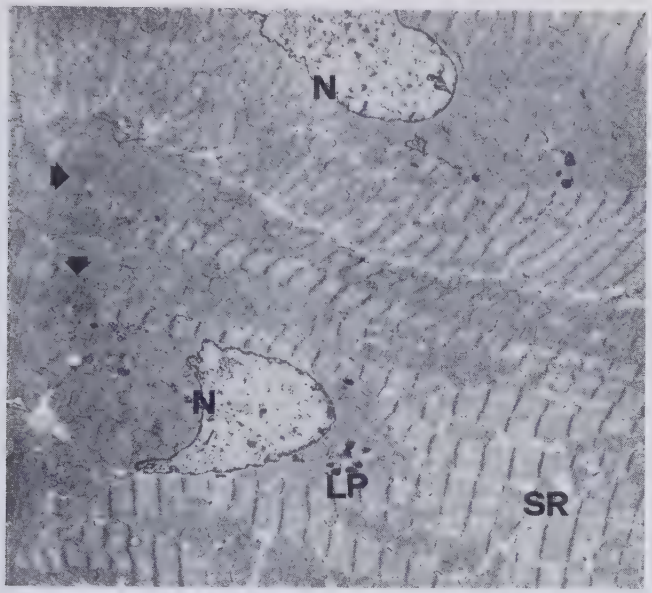

Figure 2. Myocardium from experimental animal. Longitudinal section. The two nuclei (N) have lumpy and peripherally arranged chromatin, and appear slightly swollen. The myofibrils are "thinned-out" and ruptured (below to the right). To the left, the myofibrils are necrotized and contracted (arrows). Note the dilated tubules of the sarcoplasmic reticulum (SR) and the large amount of mitochondria and lipofuscin granules (LP). Primary magnification × 1900.

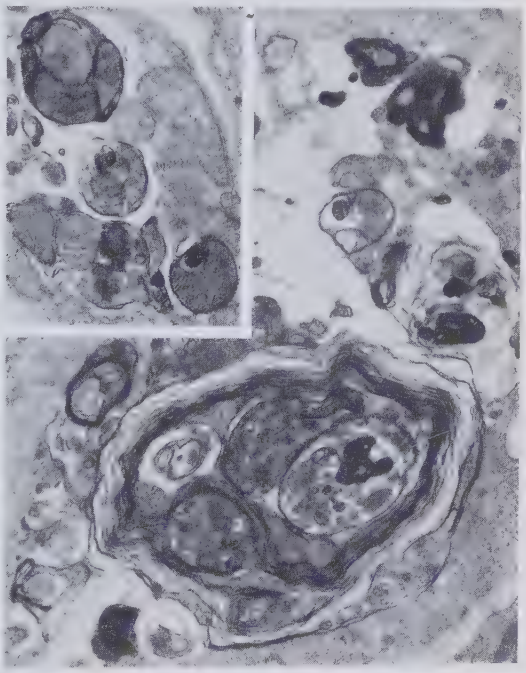

Figure 3. Myocardium from experimental animal. Typical fully developed myelin bodies. Formation of myelin bodies is illustrated by the insert, showing early myelin bodies consisting of degenerated mitochondria. Primary magnification × 9500.

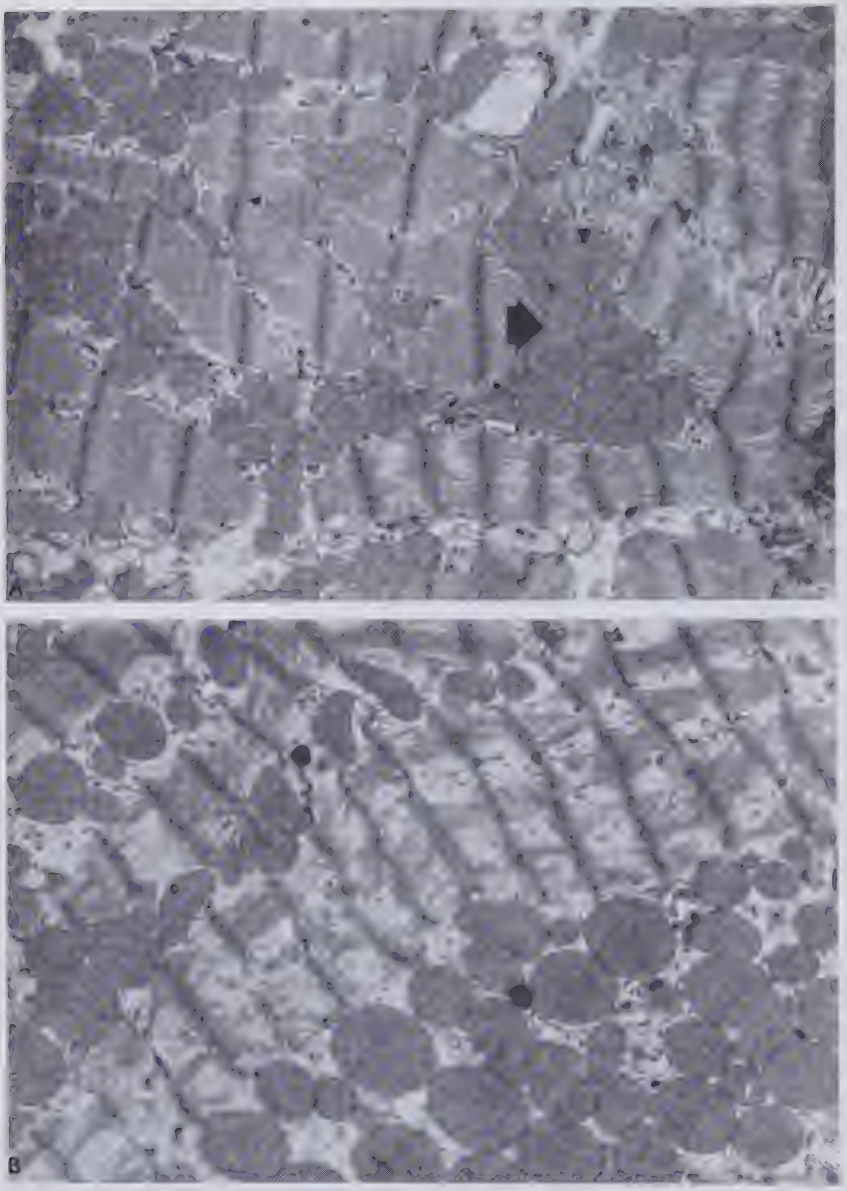

Figure 4. Myocardium from experimental animal. Photomontage showing different grades of myofibrillar injury. *A*, To the left, the Z-bands are widened and have a washed-out appearance; otherwise the fibrils are intact. To the right, the myofibrils are breaking up between the Z-bands. Note also clusters of mitochondria and "giant" mitochondria (arrow). *B*, Most of the filaments between the Z-bands have disappeared. The mitochondria are circular with homogeneous matrix.

(*Illustration continued on opposite page.*)

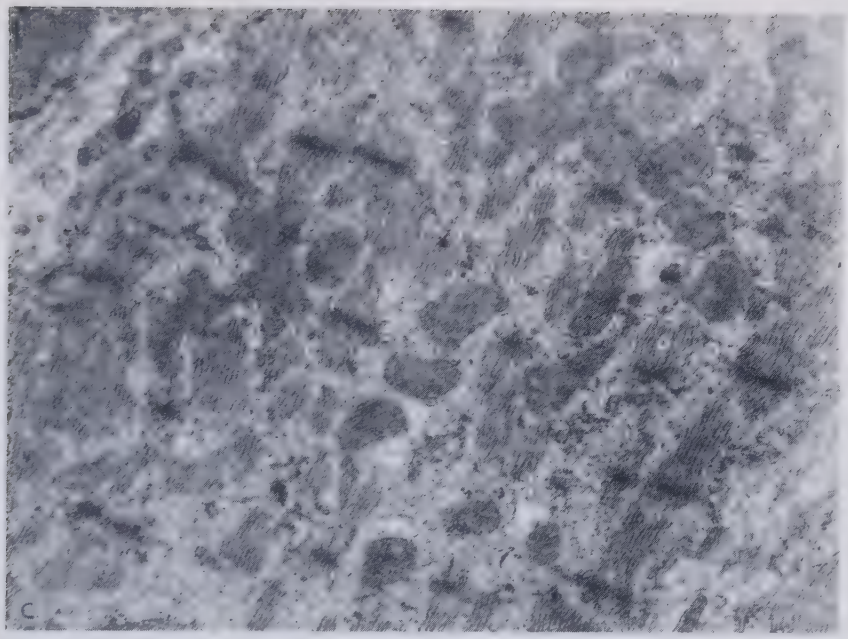

Figure 4. *Continued.* C, The myofibrils are broken into small pieces and the normal structure is completely disorganized. Note the abundant glycogen granules in the sarcoplasm. Primary magnification × 4800.

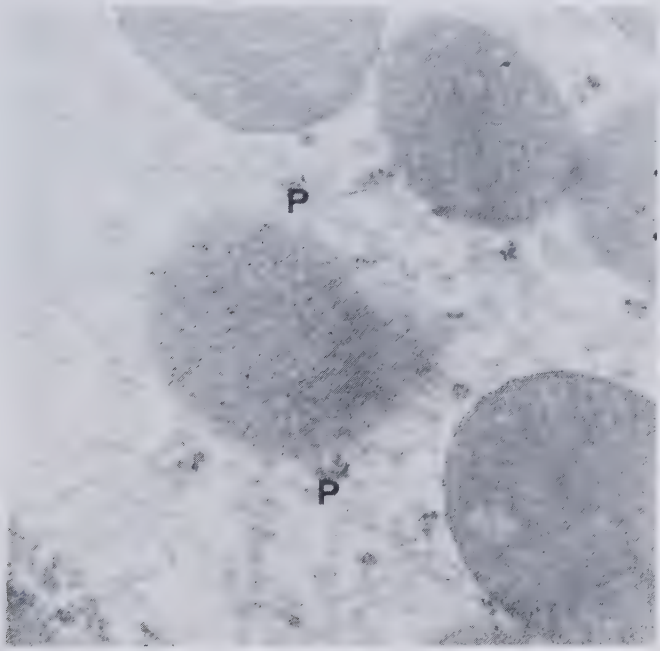

Figure 5. Myocardium from experimental animal. Mitochondria. The matrix is completely homogenized (lower right). In some mitochondria the limiting membranes are lost (center and upper right). A few polysomes (P) are seen around the mitochondria. Primary magnification × 28,000.

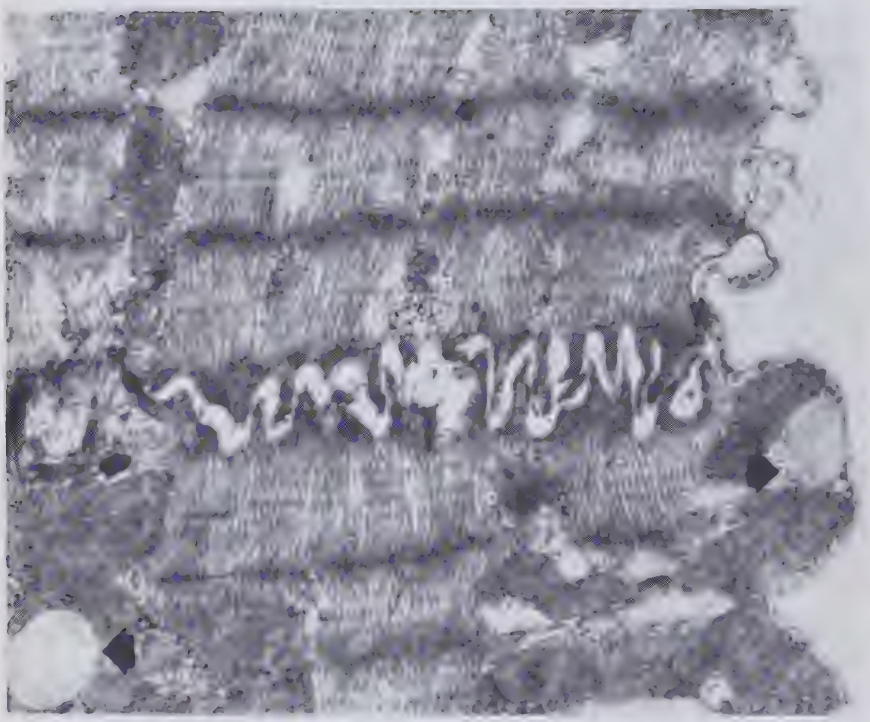

Figure 6. Myocardium from experimental animal. Contracted myofibrils and separation of the intercalated disc. Lipid droplets (arrows) are seen close to the mitochondria. Primary magnification × 9500.

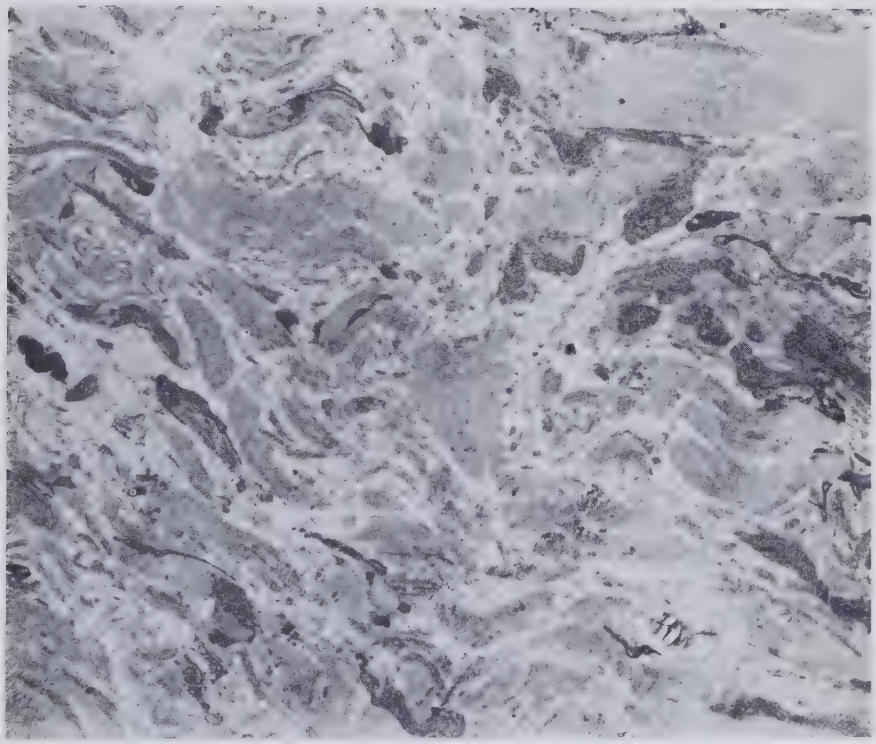

Figure 7. Myocardium from experimental animal. Scar-tissue. Between the partly hyalinized bundles of collagen fibers are seen undefined structures, probably remnants of the original tissues. Primary magnification × 9500.

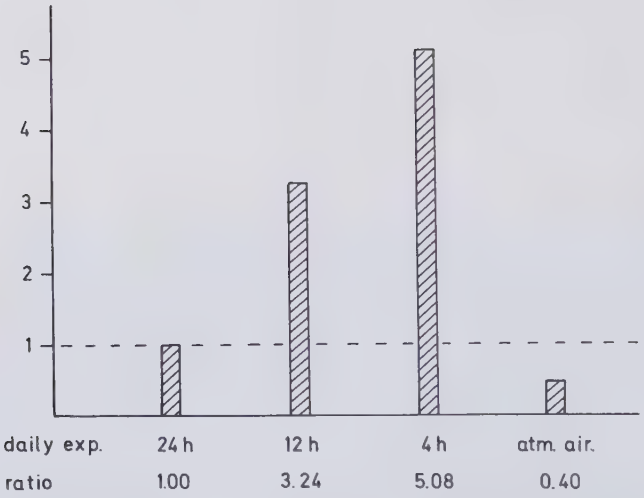

Figure 8. Relative values of aortic cholesterol in cholesterol-fed rabbits exposed to 0.018 per cent carbon monoxide for 24, 12, or 4 hours daily or to atmospheric air for 10 weeks.

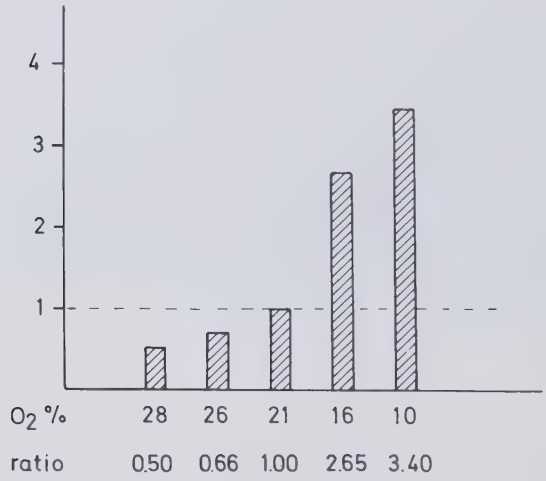

Figure 9. Relative values of aortic cholesterol in cholesterol-fed rabbits breathing air with varying oxygen content for 10 weeks.

Mild early ischemic changes are probably reversible, while later and more pronounced pathologic changes such as severe mitochondrial injury, myelin bodies and muscle necrosis are irreversible and will ultimately lead to formation of fibrotic scar-like tissue as seen in Figure 7. Abnormalities of repolarization often occur in ischemic heart muscle where necrotic and viable tissues intermingle, and there is evidence that ventricular fibrillation is generated in such areas in the periphery of a myocardial infarct.[44]

Acute cardiorespiratory effects of COHb concentrations of 2 to 25 per cent in men and dogs have been studied by Ayres and co-workers.[10] At a COHb mean of 9 per cent in 26 human subjects they found 5 per cent decrease in arterial Po_2, 20 per cent decrease in venous Po_2, 20 per cent increase in ventilation, 25 per cent increase in coronary blood flow, 10 per cent increase in cardiac output and about 50 per cent increase in alveolar-arterial oxygen difference. The decrease of arterial Po_2 is explained by assuming venous admixture to the arterial blood in connection with the left-sided displacement of the oxyhemoglobin dissociation curve produced by carbon monoxide.

Most interesting is the great increase in coronary blood flow observed in dogs as well as in human individuals, noticeable by increasing the COHb concentration to not more than 5 per cent. A similar increase in coronary blood flow is seen in hypoxemia. However, the coronary sinus oxygen tension was lowered considerably at carbon monoxide exposure, and the cardiac oxygen consumption was also reduced.[10]

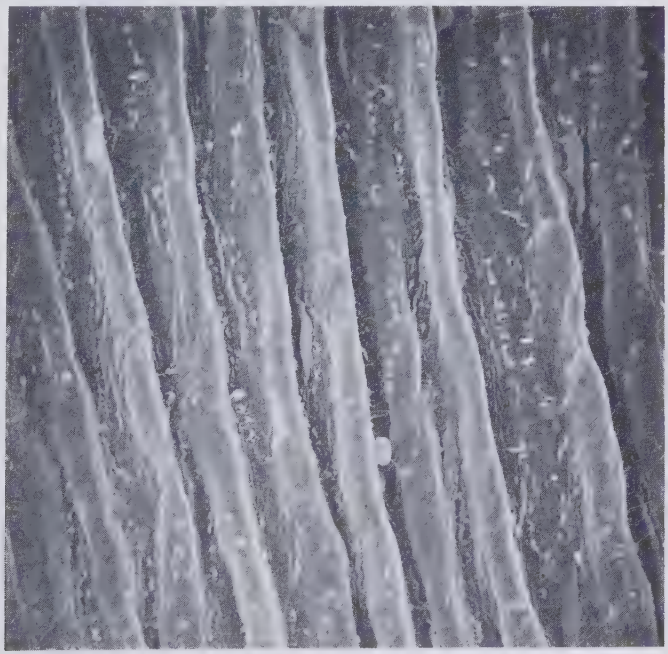

Figure 10. Surface of the distal part of the descending thoracic aorta from control rabbit showing regular intimal folds arranged longitudinally. Primary magnification × 1100.

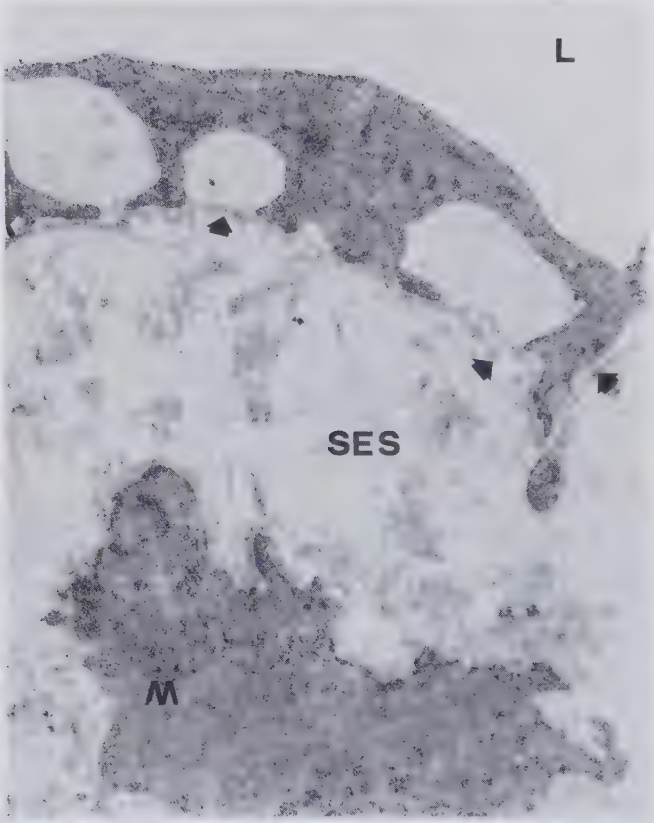

Figure 11. Endothelial cell from the distal part of the descending aorta of rabbit exposed to carbon monoxide. The subendothelial blisters between the plasma membrane and the basement membrane are separated by bridges of cytoplasma connecting the cell to the basement membrane. Note the frayed and interrupted basement membrane (arrows). A myointimal cell (M) is seen in the subendothelial space (SES) surrounded by a network of newly produced fibrils. Lumen (L). Magnification × 26,000.

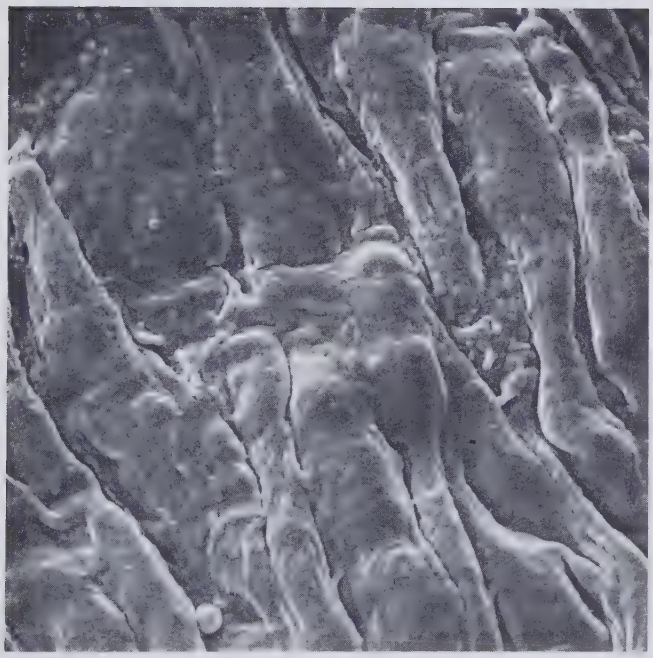

Figure 12. Surface of the distal part of the aortic arch from rabbit exposed to carbon monoxide. The normal arrangement of the intima in folds tends to disappear. Instead the surface structure exhibits a highly irregular picture with extreme swelling of the endothelial cells, which occasionally appear as "cobblestone cells" protruding into the lumen. Magnification × 1130.

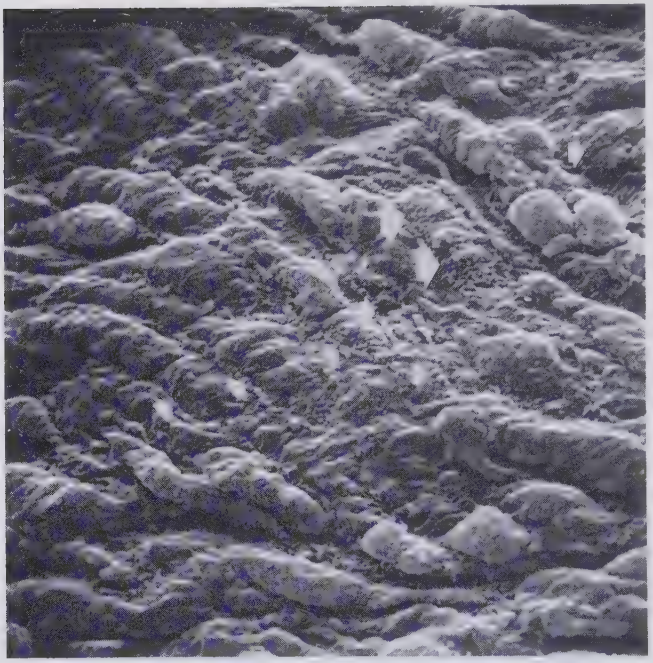

Figure 13. Surface structure of the distal part of the aortic arch from rabbit exposed to carbon monoxide. Note "cobblestone" appearance of most endothelial cells and the abundance of thrombocytes and fibrin-like material covering damaged cells (broad arrows); occasionally the coagulation material is arranged in line, possibly depicting the intercellular junctions (fine arrows). Magnification × 1130.

After 4 hours exposure to 100 ppm, resulting in COHb levels of 5 to 9 per cent, a greater myocardial stress at comparable work loads was observed in human individuals. In 7 of 26 persons aged 41 to 60 years, abnormal electrocardiograms were found, and arrhythmia developed in 2 of these. In a younger group of 12 persons aged 25 to 36 years, no abnormal electrocardiograms were seen.[46]

This demonstration of circulatory changes following acute exposure to carbon monoxide, quantitatively similar to the daily exposure of many smokers, and the demonstration of severe ultrastructural myocardial changes in rabbits following similar COHb levels maintained for 2 weeks, makes it very likely that carbon monoxide also in tobacco smokers has a serious myocardial effect.

In rabbits, *fetal development* was greatly influenced by 9 to 10 per cent and 16 to 18 per cent COHb maintained continuously during pregnancy. The major findings were a reduction in average birth weight and a highly increased neonatal mortality.[9] Increased COHb levels were suggested as the main cause of the well documented reduction of birth weight of babies delivered by smoking women.

Carbon Monoxide and Experimental and Clinical Atherosclerosis

Our findings of COHb concentrations up to 10 and 20 per cent in the blood of many smokers, especially in smokers with obliterating arterial

diseases, led to the hypothesis that it might be the carbon monoxide in tobacco smoke which was responsible for the much greater risk of developing atherosclerosis for smokers in comparison to nonsmokers. In the following, the main results of our clinical and experimental work for proving this hypothesis will be given.

For our animal experiments airtight chambers were constructed in which rabbit cages could be placed, and through which various gas mixtures could be passed. Each of the chambers we use now can hold 18 rabbit cages. The gas mixtures were made by mixing atmospheric air with carbon monoxide, oxygen and nitrogen respectively. In the first experiment cholesterol-fed rabbits were continuously exposed to carbon monoxide, 170 ppm, for 7 weeks, giving COHb concentrations around 16 per cent, and for the following 2 weeks to 340 ppm. This resulted in a cholesterol content of the aorta which was 2.5 times higher ($p < 0.001$) than in the control rabbits, which had not been exposed to carbon monoxide but were also fed cholesterol.[7] We have repeated the experiment several times and have consistently found an enhancing effect of continuous carbon monoxide exposure on cholesterol accumulation. This has now been confirmed in other laboratories,[15] also by using primates.[68] By intermittent exposure of groups of 18 rabbits each to CO, 12 or 4 hours a day, we

Figure 14. Surface of slightly elevated aortic plaque from carbon monoxide-exposed rabbit. The plaque is situated on the borderline between arch and thoracic part of the vessel. The endothelium covering the plaque is quite smooth and shows a characteristic network of fibrin-like material, possibly depicting the intercellular junctions. The plaque is surrounded by "cobblestone-structured" endothelium. Magnification × 712.

Table 3. *Average COHb Values in Atherosclerotic and Non-Atherosclerotic Smokers Chosen at Random*

	ATHEROSCLEROTIC SMOKERS		NON-ATHEROSCLEROTIC SMOKERS	
AGE GROUPS	Number	COHb (Per Cent)	Number	COHb (Per Cent)
10–19	0	–	24	2.8
20–29	0	–	127	4.2
30–39	6	11.0	192	4.6
40–49	15	6.7	210	4.6
50–59	24	7.4	125	3.7
> 60	12	4.5	61	2.9

obtained respectively 3 and 5 times higher cholesterol accumulation than by continuous exposure as demonstrated in Figure 8.

In another series of experiments (Figure 9) we exposed groups of 18 rabbits to various degrees of hypoxia (16 per cent and 10 per cent oxygen respectively for 10 weeks) and found that the cholesterol concentration in the aortic walls from the experimental groups was 3 to 3.5 times higher than in the control groups.[45] If, on the other hand, the animals were exposed to hyperoxia[41] (28 per cent and 26 per cent of oxygen respectively) the accumulation of cholesterol in aorta decreased considerably in comparison to the control animals, breathing atmospheric air. The results were highly significant ($p < 0.01$).

We have concluded from these exposure studies that lipid accumulation in the arterial walls of cholesterol-fed rabbits is highly influenced by the composition of the air the animals breathe. The accumulation is increased by hypoxia and carbon monoxide, and decreased by hyperoxia.

Macroscopically as well as microscopically there was no qualitative difference between the lesions in animals exposed to carbon monoxide and the animals exposed to hypoxia. Macroscopically it was easy to distinguish between the aortas from exposed animals and from control animals by the number and size of plaques. Similarly, the microscopic changes were more pronounced in the exposed animals, characterized by a marked lipid accumulation in intima and subintima. Also in animals not receiving cholesterol it was possible by very moderate carbon monoxide exposure (9 to 10 per cent COHb) to induce arterial lesions with a pronounced focal subendothelial edema, indistinguishable from spontaneous arteriosclerosis.[67] In the electron microscope the changes looked very dramatic.[42] Normally, the endothelial membrane in aorta from rabbits is arranged in folds, with the cells attached to the basement membrane and the internal elastic membranes beneath. By using the scanning microscope the folds are seen to be very regular (Figure 10), similar to the appearance described in man. After exposure of a rabbit to 180 ppm carbon monoxide for only 2 weeks, giving approximately 16 to 18 per cent COHb, a pronounced change occurred, demonstrated first of all by a very high degree of edema beneath the endothelial cells pushing the cells away

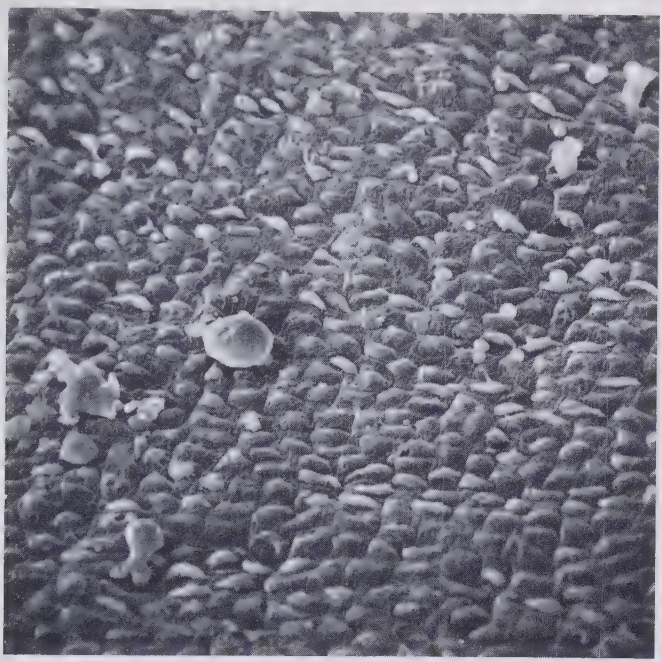

Figure 15. Surface structure of the distal part of the aortic arch from rabbit exposed for two weeks to 16 per cent oxygen in inspired air. Note the regular "cobblestone" pattern of the endothelial cells. Magnification × 570.

from the basement membrane, to which they are attached by a few strings or beams (Figure 11). The edema is dominating the picture also beneath the basement membrane, where it fills the space up to the first layers of the elastic membrane. The scanning pictures (Figs. 12 and 13) demonstrate that the regular folding arrangement disappears with the occurrences of the blisters beneath the cells. In some areas the endothelial cells were separated completely from the basement membrane by the penetrating fluid and a plaque was formed (Figure 14) where the folds had disappeared completely and the endothelial junctions were open. In other areas the cells were disrupted. Where the endothelium was very severely damaged, tiny hemorrhages could be seen, and loose aggregations of erythrocytes and thrombocytes were a regular finding at these sites. Similar but somewhat less pronounced changes were seen in aortas from rabbits exposed for 2 weeks to atmospheric air with 5 per cent nitrogen, giving an oxygen percentage of 16, corresponding to oxygen tensions occurring at an altitude of about 3500 meters.[43]

After this we had no doubt that exposure of rabbits to carbon monoxide as well as to hypoxia could result in the development of severe vascular lesions, which could not be histologically distinguished from spontaneous arteriosclerosis in these animals. Furthermore, cholesterol feeding under these conditions led to a very considerable increase of lipid accumulation.

The problem we now faced was the *pathophysiologic explanation* of

the experimental findings and the relation to the pathogenetic mechanisms in the development of atherosclerosis in man. The finding that rabbits exposed to carbon monoxide quite often had fluid with a high protein content, 3 to 4 per cent, in the serous cavities, i.e., pleura, pericardium, and peritoneum, led to the hypothesis that the arterial injuries were caused by increased permeability of the endothelial membranes, predominantly to proteins, leading to subendothelial edema as demonstrated by the microscopic and electron microscopic pictures. To evaluate this hypothesis, in 1967 we made a comparison between changes in some physiologic and biochemical parameters measured in human individuals during exposure to carbon monoxide for 10 days and later at the high altitude laboratory at Jungfraujoch in Switzerland, 3454 meters above sea level.[8] It was demonstrated that carbon monoxide exposure (20 to 25 per cent COHb) led to a 50 per cent increase of glomerular filtration rate during the first day of exposure;[54] to an increased disappearance rate from the blood of injected radionated serum I^{131} albumin,[61] and probably to an increase in capillary filtration rate measured plethysmographically on the calf.[62] This supported the hypothesis of an increased vascular permeability caused by carbon monoxide. The transvascular protein flux during carbon monoxide exposure has recently been studied in more detail in our department,[52, 53] by measuring in human individuals the disappearance rate of I^{131} albumin injected intravenously, and by following the protein flux in lymph in dogs. It was confirmed that the disappearance rate of ^{131}I albumin, after exposure of human individuals to carbon monoxide (20 to 25 per cent COHb) for 3 hours, is increased, approximately 50 per cent, and in dogs the lymph flow and the protein flux in the thoracic duct increased considerably. It was of interest that the increase in protein flux was more marked for the high molecular proteins than for the low molecular ones.[53] For example, the flux of α_2-macroglobulin (MW 830,000) in the lymph could increase 2 to 3 times more than the flux of albumin (MW 69,000). This is probably due to a carbon monoxide-induced widening of the gaps between the cells, since we have not observed increased pinocytosis in our ultrastructural studies of arterial walls in rabbits exposed to carbon monoxide. It was also possible to demonstrate[40] a correlation between COHb levels in smokers and the incidence of atherosclerotic disease as illustrated in Table 3. The individuals with atherosclerosis (coronary thrombosis, angina pectoris, or peripheral arterial obliterations) have significantly higher average COHb values than smokers without arterial disease. A further statistical evaluation of the results showed that individuals with COHb higher than 5 per cent run a 20 times higher risk of getting atherosclerosis than individuals of same sex and age with concentrations less than 3 per cent.[66]

Carbon Monoxide and Lipid Metabolism

It has been known for many years that acute exposure of animals and men to hypoxia by bleeding or by low atmospheric pressure leads to hyperlipemia. It was first noted by Boggs and Morris[16] in 1909 and later studied by various authors. The hyperlipemia involves most of the plasma lipids, the concentration of which may increase considerably during

the first 1 or 2 weeks before returning to normal values again. Also in myocardium of various species the lipid concentration increases at high altitude, owing to increased synthesis.[27] Increased synthesis may also be a cause of the hypoxic increase in plasma lipids, but no definite proof has been given. Carbon monoxide exposure also leads to hyperlipemia as shown first by Astrup et al.[7] and by Kjeldsen.[40] This was demonstrated in rabbits fed usual fodder with or without the addition of cholesterol and exposed to COHb levels between 15 and 25 per cent. We have seen this effect of carbon monoxide exposure in all our later experiments with cholesterol-fed rabbits. The carbon monoxide-induced (COHb 16 to 18 per cent) elevation of serum cholesterol has usually led to 15 to 20 per cent higher levels for the first 2 to 3 weeks in comparison to the groups not exposed to carbon monoxide, after which the levels have been approximately the same in the two groups.

To our knowledge, no studies have dealt with tissue lipids in carbon monoxide-exposed animals fed normal diets.

Many investigators have found somewhat higher serum cholesterol levels in smokers in comparison to nonsmokers,[59] usually about 10 to 15 mg. per cent, which may be explained by raised COHb levels.

OTHER ATHEROGENIC COMPOUNDS IN TOBACCO SMOKE

Toxic compounds in tobacco smoke other than nicotine and carbon monoxide may also influence the development of atherosclerosis, but no proof of this has been given so far.

A certain amount of *nitrogen oxides* (NO, NO_2, N_2O_3) is found in tobacco smoke. They are capable of entering the blood through the lungs and interact with hemoglobin, since nitrous oxide complexes of hemoglobin have been demonstrated in animals exposed to tobacco smoke.[58] The oxygen transport of hemoglobin is thus reduced further than the level corresponding to the content of COHb. In earlier investigations it was noted that blood of heavy smokers has higher total saturation values at low Po_2 values than could be explained by the presence of HbO_2 and COHb,[32] and this might well be due to the presence of such complexes.

Hydrogen cyanide does occur in cigarette smoke in ranges from 6 to 32 micrograms per puff.[70] Before detoxification to thiocyanate it might, theoretically, be able to inhibit oxidative metabolism in vessel walls and myocardium.

After the abandonment of spraying with arsenic-containing insecticides in tobacco plantations, the content of *arsenic compounds* in tobacco smoke is very low and scarcely of any pathogenetic importance for the development of atherosclerosis. There is no difference in plasma arsenic concentrations in smokers and nonsmokers and in patients with Buerger's disease, while it is up to 10 times higher in patients with endemic peripheral arteriosclerosis resulting from arsenic in drinking water.[5]

We are not aware of any other compounds in tobacco smoke which might be able to influence oxidative metabolism or in other ways influence the development of atherosclerosis.

CONCLUSIONS

Atherosclerosis

In our opinion the experimental results obtained by us and others who have investigated the atherogenic effects of moderate carbon monoxide exposure leading to COHb concentrations comparable to those found in heavy smokers strongly indicate that carbon monoxide in tobacco smoke is a toxic compound of major importance. This is supported by the finding of a correlation between COHb levels in smokers chosen at random and the incidence of atherosclerotic disease.[40] The atherosclerotic individuals had the highest average COHb values in the various age groups, and smokers with COHb values higher than 5 per cent seem to have a 20 times higher risk of getting atherosclerosis than smokers of same sex and age with values lower than 3 per cent.[66] The higher degree of atherosclerosis in inhaling smokers in comparison to non-inhaling smokers and to non-smokers, demonstrated by various autopsy studies, might therefore most likely be attributed to carbon monoxide from inhaled smoke.

The structural, biochemical, and physiologic findings in animals and human beings exposed to carbon monoxide, and their possible relationship to the development of atherosclerosis fit well with the filtration theory concerning its pathogenesis, illustrated for example by the increased endothelial permeability and the occurrence of subendothelial edema in arteries from animals exposed to carbon monoxide. It is not known how this effect of carbon monoxide comes on. It might involve local formation of plasmakinins, which increases the permeability of vessel walls to proteins. The result is, according to the ultrastructural findings, probably a widening of the gaps between the cells, and not increased pinocytosis. Hypoxemia obviously has the same effect as carbon monoxide.

In our opinion the physicomechanical concept of the filtration theory contains very much of the truth about the pathogenetic mechanisms of atherosclerosis, especially concerning the initial phase. The concept does not deny, however, the existence and the importance of metabolic and cellular processes involved, when subendothelial edema and plaque formation have occurred and when restoration takes place. In particular, the concept does not explain why cholesterol accumulates in atherosclerotic plaques to a much higher degree than other plasma components. We would like to stress that also in this respect the oxygen supply to the intima seems to be of great importance. Not only might an increased formation of lipids occur during hypoxia, but especially the removal of already accumulated lipids seems to be enhanced by hyperoxia (26 per cent oxygen) according to recent unpublished experimental results.[6] It might be supposed that exposure to hypoxia or to carbon monoxide has an opposite effect.

Since hypoxia in principle gives vascular changes similar to those of carbon monoxide exposure it may be concluded that oxygen deprivation is the primary effect of carbon monoxide. It affects the oxygen transport of hemoglobin and myoglobin as well as the function of enzyme systems

where oxygen and carbon monoxide act competitively. The presence of nitrous oxides and hydrogen cyanide in tobacco smoke may further add to the oxygen depriving effects of carbon monoxide. The hypoxic effects are aggravated by the insufficiency of the cardioventilatory responses to carbon monoxide exposure, which are less pronounced than to hypoxia exposure, and do not prevent a decrease in tissue oxygen tensions.

Cardiomyopathy and Sudden Death

Despite great increase in coronary blood flow after carbon monoxide exposure, the coronary sinus oxygen tension decreases in animals and human beings, and severe ultrastructural damage of the myocardium has been observed in rabbits after 2 weeks exposure to carbon monoxide, leading to 16 to 18 per cent COHb. Similar effects may be expected in man exposed to carbon monoxide. The myocardial damage will, of course, be more pronounced when blood flow in the coronary arteries, arterioles or capillaries is impeded, owing to luminal narrowing by subendothelial edema or atheromata.

Carbon monoxide-induced myocardiopathy is probably of essential importance for the increased incidence of heart disease in smokers in comparison to nonsmokers. It might partly explain the occurrence of angina pectoris in smokers, and the increased tendency to arrhythmia after administration of either nicotine or carbon monoxide, when myocardial damage is present, might explain at least some cases of sudden, unexpected death in smokers, when no thrombi can be found.

Nicotine Versus Carbon Monoxide

Many experimental studies have shown that nicotine, when administered alone in amounts relatively much higher than the nicotine uptake by a smoker, has no atherogenic effect, but may cause necrosis and calcification in the middle layers of aorta and arteries, thus being of importance for the development of the nonobliterating Mönckeberg type of arteriosclerosis in man. Since COHb levels similar to those found in heavy smokers cause atherosclerotic changes and myocardial damage in animals, we conclude that carbon monoxide, and not nicotine, is the toxic compound of major importance for the increased risk of smokers to develop atherosclerosis and heart disease. Nicotine seems not to have a synergistic effect on the carbon monoxide-enhanced accumulation of lipids in arterial walls, but is probably of importance for the occurrence of arrhythmia in smokers leading to sudden death, and its vasoconstrictory effects in certain regions may further impair oxygen supply in smokers with high COHb levels.

Future Studies

The effect of carbon monoxide and hypoxia on endothelial permeability should be investigated further, biochemically as well as physiologically, and the molecular processes involved should be identified.

The effect of carbon monoxide, hypoxia, and hyperoxia on lipid metabolism in arterial walls should be further evaluated.

Epidemiological studies of the risk of smokers to develop athero-

sclerosis and heart diseases might benefit from including measurements of COHb concentrations after smoking.

COHb concentrations measured after smoking may help to discourage smoking, by indicating the risk for the smoker of developing atherosclerosis and cardiomyopathy.

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Hyperlipidemia and Coronary Artery Disease

Principles of Diet and Drug Treatment

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Early experimental production of hypercholesterolemia and atherosclerotic arterial lesions in rabbits by cholesterol and oil feeding[3] has continued to call attention to the role of dietary fat and cholesterol in raising the serum cholesterol level and the development of coronary artery disease in man. This diet-cholesterol-atherosclerosis hypothesis has been intensively investigated by means of comparative and prospective epidemiologic studies[24, 25, 37] and field trials of low cholesterol, high polyunsaturated fat diets.[10, 12, 45, 47]

When controlled metabolic and biochemical methods are applied to the study of individual patients,[1, 14] it is found that hypercholesterolemia may constitute one of the manifestations of a number of inherited diseases and metabolic abnormalities. Depending upon the underlying genetic-metabolic abnormality of the individual subject, hypercholesterolemia may be relatively "pure" or may occur secondary to elevation of other plasma lipids, especially triglycerides.[27] Since hypercholesterolemia may have various causes, there is little ground to believe that it would respond to one type of treatment. Recent supplementation of cholesterol and triglyceride determinations with lipoprotein analysis[34] has helped in differentiating hypercholesterolemia into distinct types of hyperlipoproteinemia (hyperlipidemia), on the basis of the underlying genetic metabolic defect.[14] The purposes of this communication are: (1) to describe those types of hyperlipoproteinemia that are known to be closely associated with development of atherosclerosis, and (2) to discuss the principles of diet and drug therapy recommended for each of these disorders.

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HYPERLIPOPROTEINEMIA (HYPERLIPIDEMIA, HYPERCHOLESTEROLEMIA)

By correlating characteristic clinical manifestations with appropriate laboratory findings (plasma lipid-lipoprotein determinations) and similar data from the patient's family members, Fredrickson, Levy, and Lees have attempted to classify the various types of plasma lipid abnormalities into hyperlipoproteinemia, Types I through V.[11] Although the proposed system may require further modifications as experience is gained, its use for defining familial hyperlipoproteinemias was well conceived and has received widespread support. In this connection, it might be worthwhile to re-emphasize the generally known fact that not infrequently hyperlipoproteinemias similar to the genetic types may occur secondary to a number of hormonal, metabolic, and nutritional disturbances. Some of the more common diseases which tend to cause secondary hyperlipoproteinemias include diabetes mellitus, nephrotic syndrome, hypothyroidism, alcohol induction and faulty dietary habits, as well as use of oral contraceptives. In some cases it may be difficult to differentiate a metabolically or nutritionally induced hyperlipoproteinemia from one or the other familial types with certainty. Perhaps in certain instances a clear-cut differentiation of primary from secondary hyperlipoproteinemia is not crucial in determining the risk of vascular complications, however, the exercise is helpful in the prognosis and management of the various disorders.

Frequency Distribution of Different Hyperlipoproteinemias Among Hyperlipidemic Atherosclerotic Patients

A survey of the frequency distribution of different types of hyperlipoproteinemia among atherosclerotic patients with elevated serum lipids would help in the selection of those that appear to have the closest relationship to atherosclerosis for more careful examination. The data obtained through lipoprotein analyses of a random series of 334 patients are

Table 1. *Incidence of Different Types of Hyperlipoproteinemia in 334 Atherosclerotic Patients with Hyperlipidemia*

LIPOPROTEIN PHENOTYPES[14]	-LIPO-PROTEIN	PRE -LIPO-PROTEIN	CHYLO-MICRON	NUMBER (% OF LIPEMIC PATIENTS)
I	−	−	+	0 (0)
II_a	+	−	−	34 (10.2)
(II_b)	+	+	−	142 (42.5)
III	+ (abnormal)	+	±	3 (0.9)
IV	−	+	−	150 (44.9)
V	−	+	+	5 (1.5)
Total				334

+ = increase
− = normal range
± = slight increase

presented in Table 1. Briefly, these studies showed the following: (1) Simple elevation of cholesterol or low density betalipoprotein (LDL) (Type II_a) was observed in about 10 per cent of the patients;[13] (2) a significant segment of this group, 142 patients (42.5 per cent), showed combined hyperlipidema and an increase in LDL with a concomitant increase in very low density prebetalipoprotein (VLDL), Type II_b;[6] (3) a simple increase in triglycerides was present in 150 patients (44.9 per cent) of the group (Type IV). Thus practically all atherosclerotic patients with hyperlipidemia manifested an increase in LDL (Type II_a) or VLDL (Type IV), or both (Type II_b). An essentially similar distribution of hyperlipoproteinemia has been reported on a carefully studied series of patients with angiographically proved coronary artery disease.[14] The data also coincide well with the three recently defined types of hyperlipidemia in coronary heart disease.[15a] Therefore, in this discussion, primary emphasis will be placed upon Types II_a, II_b, and Type IV lipoprotein disorders.

HYPERCHOLESTEROLEMIA AND HYPERBETALIPOPROTEINEMIA (TYPE II HYPERLIPOPROTEINEMIA)

Although much interest has centered around familial hyperlipoproteinemia, most clinically encountered Type II abnormality with its associated hypercholesterolemia is secondary to a number of common metabolic and hormonal disturbances. Among the most common but less obvious causes are hypofunction of the thyroid gland and consumption of excessive amounts of saturated fats rich in short-chain and medium-chain triglycerides and cholesterol. Other causes, such as obstructive liver disease, nephrotic syndrome, and dysproteinemia, are usually recognized readily.

Primary Type II hyperlipoproteinemia is perhaps the most common kind of familial hypercholesterolemia. It is characterized by an increase of low density beta-lipoprotein (LDL) concentration. A sizable portion of atherosclerotic patients with hyperbetalipoproteinemia in our series (Table 1) are found to have a mild to moderate concomitant increase in very low density prebetalipoprotein (VLDL), with variable degrees of hypertriglyceridemia (Type II_b) or combined hyperlipidemia.[15a] Although the genetic and metabolic implications of Type II_b are still uncertain, current experience indicates that patients with this type of abnormality are susceptible to premature atherosclerosis in a way generally similar to those with an isolated LDL elevation (Type II_a). Fredrickson, Levy, and Lees have suggested cut-off points for high total serum cholesterol and LDL-cholesterol levels to differentiate familiar Type II individuals in various age groups from the corresponding unaffected members of the population.[14]

The association of accelerated development of severe atherosclerosis with premature vascular catastrophe among Type II homozygotes is generally known. Data collected from the familial survey of a large kindred

led Harlan and his associates to conclude that incidence of atherosclerosis is not unduly high among the Type II heterozygotes.[17] On the other hand, Jensen and his associates found that among 181 affected members of 11 Type II hypercholesterolemic Danish families, coronary disease was diagnosed in 59 (32.5 per cent), while among the 150 normocholesterolemic family members, coronary disease was present in only 2 (1.3 per cent).[22] Slack also reported increased risk of ischemic heart disease in a series of patients with Type II disease. Among the affected males the chance of a first attack of ischemic heart disease was 5.4 per cent by age 30, and 51.4 per cent by age 60. In females the risks were somewhat lower, but were much higher than in normolipemic subjects.[44]

Recent investigations suggest that Type II is detectable in young children even at birth by study of cord blood.[15] Application of current knowledge and recently developed methods for diagnosis of this familial disease with greatly increased risk for vascular disease is urged. A number of diet and drug programs are being developed and evaluated in the attempt to prevent the accelerated development of atherosclerosis. An effective LDL lowering program should be prescribed for pediatric and young adult populations with Type II abnormality before significant anatomic atherosclerosis develops.

HYPERTRIGLYCERIDEMIA AND HYPERPREBETALIPOPROTEINEMIA (TYPE IV HYPERLIPOPROTEINEMIA)

Just as hyperbetalipoproteinemia is the most common kind of familial hyperlipoproteinemia, hyperprebetalipoproteinemia (VLDL increase) and its associated hypertriglyceridemia is an abnormality frequently found in association with several common metabolic and nutritional diseases. This VLDL abnormality is demonstrable in high percentage of insulin-dependent diabetic children before they receive treatment.[9] It is also observed in many older, overweight, insulin-resistant diabetics, with poor control of carbohydrate metabolism.[43]

Although alcohol consumption usually does not induce a persistent serum lipid elevation in normolipemic subjects, in many instances it may act to aggravate an underlying Type IV or Type V abnormality.[30] Because of the difficulty in making a clear-cut distinction between primary and secondary hyperprebetalipoproteinemia, relative susceptibility of patients with one or the other types of lipid abnormality to the hyperlipemic effect of alcohol has not been adequately determined.[21, 23, 36]

A mild to moderate increase in plasma VLDL concentration and its associated hypertriglyceridemia probably constitutes the commonest type of clinical hyperlipoproteinemia. In the affluent society, prolonged overnutrition causes adiposity, abnormal insulin mechanism, carbohydrate intolerance, and hypertriglyceridemia in susceptible individuals.[25–27] On the other hand, a number of retrospective studies have indicated a close association between hyperprebetalipoproteinemia (hypertriglyceridemia) and coronary artery disease.[11, 28–30] Since Type IV hyperlipoproteinemia with its underlying metabolic derangement generally requires

time to develop, it differs from genetic Type II abnormality in that it contributes rather lightly to premature atherosclerosis while it exerts its atherosclerotic influence chiefly upon the large number of middle and older aged persons. Furthermore, a large number of atherosclerotic patients with Type II abnormality is burdened with a concomitant hyperprebetalipoproteinemia (Type II_b in Table 1) of either genetic or environmental origin.

"FLOATING" BETALIPOPROTEINEMIA (TYPE III)

Type III hyperlipoproteinemia (Type III) is also associated with premature vascular disease with apparent predilection for the peripheral vessels.[7, 35] It is a relatively uncommon abnormality but appears to be readily amenable to specific diet and drug therapy.[35, 49] Patients with this type of lipid abnormality may help to supply answer to the question of whether successful control of a hyperlipoproteinemic state could achieve an appreciable regression of the pre-existing atherosclerotic lesion. The phenotypic characteristic of this condition lies in the demonstration of an abnormally low density LDL. The abnormal electrophoretic beta migrating lipoproteins float at a density <1.006 instead of the usual density of <1.063. A combination of electrophoresis and ultracentrifugation is currently required to establish the correct diagnosis. Development of new, simpler laboratory methods for isolating "floating" beta and to differentiate it from normal LDL and VLDL would aid in uncovering many of the as yet undiagnosed cases.

MANAGEMENT OF LIPOPROTEIN ABNORMALITIES MOST FREQUENTLY ENCOUNTERED IN ATHEROSCLEROTIC PATIENTS

Available evidences indicate that: (1) a number of disease states may cause disturbance in plasma lipid transport and metabolism to develop specific types of hyperlipoproteinemia, and (2) the basic genetic and metabolic abnormalities which result in increases in either LDL or VLDL or both appear to be conducive to atherogenesis. Therefore, one of the key therapeutic approaches toward primary and secondary prevention of atherosclerosis is to develop effective measures for controlling the underlying metabolic abnormalities leading to LDL and VLDL elevations.

Plasma lipid elevations secondary to a variety of diseases are frequently encountered in patients with and without clinical atherosclerosis. In these cases, the plasma lipid abnormality is corrected following appropriate management of the primary metabolic disorders. The diet and drug therapy recommended for treatment of patients with LDL and VLDL elevations which are not related to a known metabolic or nutritional disorder are briefly presented in the following:

Diet

Dietary management should constitute the primary approach to hyperlipoproteinemia. The basic metabolic and biochemical mechanisms

Table 2. *Principles of Dietary Treatment Adopted for Patients with Hyperbetalipoproteinemia (Type II_a Hyperlipoproteinemia) in this Clinic*

1. Reduce total daily cholesterol intake to < 300 mg.
2. Use polyunsaturated oils for food preparation
3. Reduce dietary saturated fats, especially those with high short-chain and medium-chain triglyceride content (butter fat and coconut oil)
4. Avoid excessive simple-carbohydrates

of hyperbetalipoproteinemia (LDL increase) are in the process of being elucidated. Opinion is divided between an increased production and a decreased removal of LDL to account for its increase in the circulation. Although the latter mechanism is favored by recent LDL turnover studies performed on patients with familial Type II abnormality, failure in feedback suppression of cholesterol biosynthesis has been demonstrated by Brown and associates.[8a] It is likely that both mechanisms may contribute to a variable extent in the hyperbetalipoproteinemia of each patient. Based on this understanding, it is rationalized that a diet designed to restrict the use of foods with (1) high cholesterol content, (2) excessive carbohydrate calories, especially simple carbohydrates, and (3) oil and fats rich in saturated short-chain and medium-chain triglycerides, should help to limit exogenous cholesterol absorption and to reduce the availability of glucose and 2-carbon fragment precursors for *de novo* fatty acid cholesterol and triglyceride synthesis. At the same time, reduction in saturated short-chain and medium-chain triglyceride intake would also serve to increase the P/S ratio of dietary fat without added polyunsaturates. Although only a modest hypocholesterolemic effect in patients with LDL problems can be expected from the dietary therapy (Table 2), the regimen helps to set the stage for hypocholesterolemic drugs to exert their optimal effects to bring this hard-to-manage type of hypercholesterolemia under control.

Hyperprebetalipoproteinemia (VLDL increase) is a feature common to Types II_b, III, IV, and V hyperlipoproteinemia. Since most mammalian organisms are adapted to convert excessive carbohydrate calories into lipids (endogenous VLDL), the therapeutic diet is designed to lower the generally high carbohydrate intake of most patients. Examples of the major groups of food to be avoided or drastically reduced are listed in Table 3. A total of 125 gm. (500 K calories) of carbohydrate per day is con-

Table 3. *Major Groups of Food to be Avoided or Severely Restricted by Patients with Hyperprebetalipoproteinemia (Type IV Hyperlipoproteinemia)*

1. Simple-carbohydrates (sugar and sugar-containing foods)
2. All alcoholic beverages
3. Saturated fats and oils rich in short and medium triglycerides (butter fat and coconut oil)
4. Between meal snacks of dehydrated starchy foods (crackers, chips, nuts, pretzels)

sidered to be adequate for maintenance of good nutrition.[39] Therefore, the expectations are that: (1) the regimen would lower the habitually high carbohydrate intake of the patient but would not lower it to unphysiological levels; (2) it will serve to reduce the glucose and other precursors for endogenous lipogenesis; (3) the diet can cause a significant weight loss through reduction of fat cell size and restore cellular sensitivity to insulin.[42]

In recent years much interest has been focused upon the role of different kinds of carbohydrates in hypertriglyceridemia (hyperprebetalipoproteinemia).[5, 16, 31, 48] Because of the kind of sugar used (glucose vs. sucrose and fructose for example), the type of subjects studied (normolipemic vs. a variety of hyperlipidemics), the kind of experimental diet employed (saturated fat and cholesterol content), and other not well understood individual metabolic differences,[19] a more potent lipogenic activity of sucrose than that of starch has not been regularly demonstrated. When the experimental design was made by taking some of these factors into consideration, a more potent hyperlipemic effect of sucrose than that of starch was elicited in Types IV and V hyperlipemic patients when sucrose was ingested in a high saturated fat, high cholesterol diet.[4] Furthermore, sugar-containing foods are high in total and carbohydrate calories and low in satiety value. Experiences gained from controlled metabolic ward studies indicate that a practical method of limiting the daily carbohydrate intake to about 125 gm. per day is to omit all simple carbohydrates (sucrose, syrups, honey, fructose, and lactose) and all sugar-containing foods from the diet.[28] These studies also show that unless snacks of dehydrated starchy foods are used, the amount of cooked starches consumed in three regular-sized meals is generally well tolerated by most patients including those who are prone to the development of hyperprebetalipoproteinemia.

Alcohol is known to exert a powerful influence upon lipid metabolism of all persons and that of patients prone to VLDL elevation in particular.[30] Besides contributing to additional calories, alcohol also acts to accentuate hypertriglyceridemia by stimulating the fatty acid release from the adipose tissue, increasing VLDL synthesis in the liver, and retarding removal of VLDL and chylomicrons from the circulation.[21, 23, 36] Therefore, alcohol restriction should constitute one of the primary requirements for the control of hypertriglyceridemia (VLDL increase) in many patients with Types II_b, III, IV, and V hyperlipoproteinemia.

Restriction of fat and oils with high short-chain and medium-chain triglyceride content is also recommended in order to limit the supply of precursors for endogenous VLDL synthesis. In general, patients with a predominant VLDL elevation tend to handle the average daily cholesterol intake without difficulty.

Drug Therapy

LDL elevation in primary Type II disease is most resistant to treatment but the outlook for its effective control has brightened considerably in the past few years with the introduction of cholestyramine[20] and, more recently, Colestipol[40] and para-aminosalicylic acid (PAS).

The first two drugs act to hasten cholesterol degradation by binding

Table 4. *Side Effects of Bile Acid Sequestrants (Cholestyramine and Colestipol) Observed in 54 Patients*

SYMPTOMS	NO. OF PATIENTS ON COLESTIPOL (23) WITH SYMPTOMS	NO. OF PATIENTS ON CHOLESTYRAMINE (31) WITH SYMPTOMS
Difficult to swallow including bulkiness	3	2
Fullness and gaseousness	2	3
Constipation	2	4
Watery diarrhea (initially)	0	2
Cholelithiasis	0	1 (?)
Renal calculi	0	0

with bile acids in the intestinal tract and preventing their absorption. In a series of 54 adult Type II heterozygotes, 20 to 30 gm. of either drug has been administered in conjunction with the therapeutic diet described above. LDL-cholesterol reduction ranging from 42 to 62 per cent of pretreatment levels was sustained by 46 patients for 9 to 18 months. Early experiences suggest that 24 to 36 gm. doses of either drug can be tolerated by most patients without major side effects, including steatorrhea. Side effects are principally those of gastrointestinal disturbance, which tend to subside following a period of adaptation. A list of side effects encountered by our patients is presented in Table 4. Type II abnormality also responds well to adequate doses of D-thyroxin, PAS, or nicotinic acid. When fairly large doses of D-thyroxin are used, the patient should be watched for aggravation of angina pectoris and related complications of myocardial ischemia. Except for minor gastrointestinal symptoms, PAS is generally well tolerated. Pharmacologically effective doses of nicotinic acid may cause nausea and vomiting in a number of patients. Smaller nontoxic doses of nicotinic acid can be prescribed to augment the hypocholesterolemic effect of bile acid sequestrant for the control of severe forms of familial Type II hyperbetalipoproteinemia.[38] Clofibrate is far less effective than bile acid sequestrants in documented primary Type II patients.

Hyperprebetalipoproteinemic (hypertriglyceridemic) patients are often overweight, with altered carbohydrate metabolism and insulin ac-

Table 5. *Drugs Recommended for Treatment of Hyperlipidemias Closely Associated with Atherosclerosis*

HYPERLIPOPROTEINEMIA, TYPE	DRUG(S) OF CHOICE
II_a	Cholestyramine or Colestipol; either in combination with nicotinic acid; para-aminosalicylic acid (PAS)
II_b	Cholestyramine or Colestipol; either in combination with nicotinic acid or PAS
III	Clofibrate
IV	Clofibrate in selected cases

tivity. In the great majority of cases, the metabolic disorder as manifested in VLDL elevation generally responds well to the use of diet restricted in simple-carbohydrates and saturated fats, and weight reduction. Although clofibrate, D-thyroxin, and nicotinic acid have been prescribed for the disturbance with variable degrees of success, no consistently satisfactory long-term effect has been obtained without the benefit of proper dietary regulation. Interestingly enough, while cholestyramine is useful in treating patients with LDL elevation, the drug has little effect upon VLDL abnormality and may even act in some unknown manner to exaggerate the hypertriglyceridemia.

Type III hyperlipoproteinemia seems to respond exceptionally well to clofibrate, although therapeutic doses of D-thyroxin or nicotinic acid are also effective, if they are tolerated by the individual. As in patients with VLDL problem, administration of clofibrate should be combined with reduced carbohydrate and cholesterol caloric intake for optimal control of the abnormal lipid metabolism.[46] The drugs of choice recommended for the few hyperlipidemias closely associated with atherosclerosis are listed in Table 5.

EVALUATION OF THE EFFECTIVENESS OF THERAPY

Through follow-up study of 184 well-motivated atherosclerotic patients with LDL or VLDL abnormality or both for 4 to 6 years,[29] it is learned that the described hyperlipoproteinemia type-oriented diet and drug therapy program is successful in achieving the following measurable changes: (1) moderate to marked loss of adiposity, (2) improvement of glucose tolerance, (3) reversion of abnormal serum insulin activity toward normal and (4) a sustained reduction in plasma LDL, VLDL and chylomicron and "floating" beta-lipoprotein concentrations, accompanied by lowered serum cholesterol or triglyceride level or both.

Changes in clinical status include: slow disappearance of xanthelasma, cutaneous and tendinous xanthomata, and impressive improvement in symptoms of vascular ischemia. Objective evidence of regression of chronic arterial lesions has been difficult to obtain. Efforts have been made to secure angiographic data before and 2 to 3 years after the institution of therapy. These studies are supplemented by quantification of exercise tolerance[41] and visualization of conjunctival and nailfold capillaries.[32] Information gleaned from a still rather limited number of patients subjected to a follow-up arteriogram suggests that the therapy may have retarded the progression of arterial lesions to abide time for readjustment of the ischemic circulatory bed. The x-ray evidence of mere retardation in progression of vascular lesions seems to confer relief of ischemia and protection against recurrence of atherosclerotic complications to keep the mortality and morbidity of this series of patients at encouragingly low rates. An experimental plan for 5 to 10 year follow-up on a larger group of patients with a randomized group of controls is needed for an accurate evaluation of the effectiveness of hypolipemic therapy in the prevention of atherosclerosis and its vascular complications.

SUMMARY

It has been customary to associate different degrees of hypercholesterolemia or hypertriglyceridemia with the development of atherosclerosis. Plasma lipoprotein analysis made in conjunction with the lipid determinations is helpful in revealing that: (a) practically all hyperlipidemic and atherosclerotic patients would manifest an increase in beta-lipoprotein (LDL) or in prebeta-lipoproteins (VLDL) or in both fractions. (b) Since LDL has a high cholesterol content and VLDL is relatively rich in triglycerides, an increase in one or the other or both lipoprotein species would result in various types of serum cholesterol and/or triglyceride elevations.

A small number of hyperlipidemic patients are found to have the interesting "floating" beta abnormality. Its ready response to a low cholesterol, weight reduction diet and clofibrate and nicotinic acid should encourage physicians to make special efforts to establish the correct diagnosis.

Hyperbetalipoproteinemia (Type II abnormality) can best be controlled by low cholesterol and low saturated and high polyunsaturated fat diet supplemented by the administration of a bile acid sequestrant.

Successful control of hyperprebetalipoproteinemia (occurring alone or in combination with hyperbetalipoproteinemia) depends largely on restriction of simple carbohydrates, alcohol, and excessive saturated fat intake to achieve weight reduction. Its response to drug treatment without the benefit of dietary regulation is inconsistent at best.

Preliminary data suggest that satisfactory long term control of the abnormal lipid metabolism may constitute an effective means in primary and secondary prevention of atherosclerosis.

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The Role of Cholesterol in Coronary Atherogenesis

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Death as a consequence of a compromised circulation to the brain, heart, kidneys, and limbs is the most potent force of mortality operating in the world today, particularly in affluent societies. There is much to suggest that modification of life style by modern technology—which has replaced muscle power with machines and has provided a surfeit of rich food and drink while at the same time shrinking opportunities for physical exercise—has exacted an increased toll in cardiovascular mortality. The facts that atherosclerosis is the chief killer of mankind and that alteration of our ecology may be promoting it demand some kind of action.

Prevention of any disease requires at the very least some knowledge of the circumstances under which it arises, evolves, and terminates fatally in human populations. Such insight has accumulated in reasonably undistorted fashion from prospective epidemiologic studies such as the Framingham study. The characteristics of the potential coronary victim have been discerned and factors which increase risk identified. Based on estimates of the magnitude of the risk associated with some of these factors, singly and in combination, a profile of the potential coronary candidate can be derived which can predict disease over a wide range of probabilities—as much as 13-fold (Fig. 1). In short, a portrait of the potential coronary candidate, at first hazy, but now increasingly sharp, has arisen.[12]

Atherosclerosis, and coronary heart disease in particular, is a disease that appears to evolve under the influence of multiple contributors and it is an oversimplification to focus on one factor to the exclusion of others. In fact, the concept of a single essential cause for any chronic disease has fallen into justified disrepute. Such a conceptualization is much too narrow. To date, no essential factor, without which the disease fails to occur, has been implicated in atherosclerotic disease. The disease appears to be ubiquitous in man beyond age 20 and can be looked upon as a concomitant of aging. Propensity to this vascular affliction can even be regarded solely as a function of the type of vasculature inherited. There is a good

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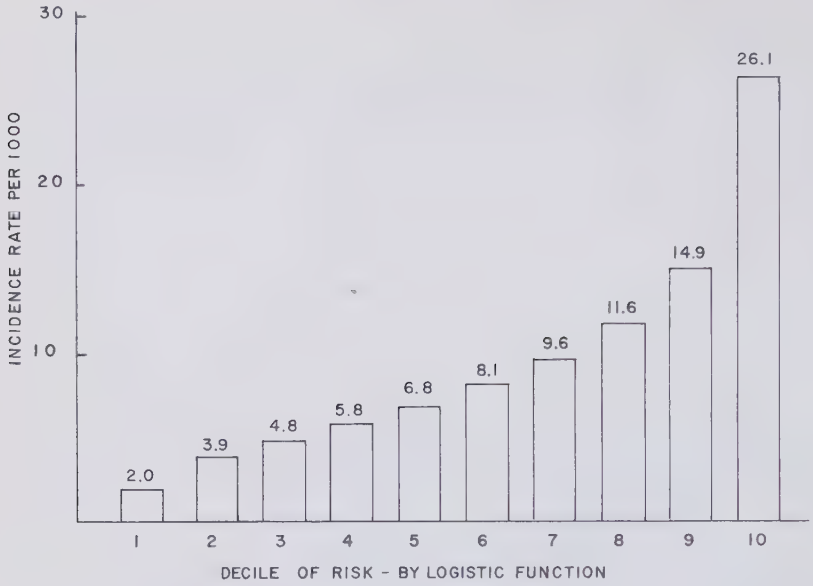

Figure 1. Average annual incidence of coronary heart disease according to decile of risk. 16-Year follow-up, men aged 45 to 54, Framingham Study. Note: The probability of coronary heart disease developing is defined by a logistic function using systolic and diastolic blood pressure, number of cigarettes per day, electrocardiographic signs of left ventricular hypertrophy, serum cholesterol, and glucose intolerance.

deal of evidence to support this pessimistic contention. While the general tendency to deposit lipid in the arterial intima may to a great extent be determined by the level of blood lipids and the blood pressure, dynamics of flow, arterial caliber, and the integrity of the vascular intima powerfully influence where atheromata will form.[6, 15, 20] The same lipid-laden blood bathes the intima of the veins and pulmonary arterial vasculature; yet atheromata do not develop in these unless turbulence or pressures such as those in the systemic arterial circulation are produced by abnormality. Failing this, veins and pulmonary arteries can be quite tortuous and still escape atheromatosis. Also, while almost everyone appears to have enough lipid to develop atheromata under the right circumstances, and local factors play a decisive role as to whether and where they will form, it is a fact that the rate of atheroma formation is proportional to the blood lipid and blood pressure values experimentally induced in animals[8, 10, 14] and spontaneously observed in man.[5]

To contend that the architecture of the vasculature is the sole or even the chief determinant of atheroma formation under these circumstances is as faulty in logic as to invoke cholesterol as the sole determinant of atheromatosis. Host susceptibility to any noxious influence, including cholesterol, varies over a wide range, and resistance to atherogenic precursors varies over a wide range.

A number of epidemiologic observations bear on the possibility of genetic influences including the sex ratio, racial variation, familial aggregation, familial hyperlipoproteinemias, and age trends, among others. Atherosclerotic disease may be looked upon basically as a concomitant of

aging and can be regarded as preventable only to the extent that we can retard the "aging process." As in almost every other "chronic and degenerative disease," age is a powerful variable and the precocious occurrence of atherosclerosis in young persons can be regarded as simply the extreme or tail of the normal distribution. All of the known "risk factors" taken together, while related to age, cannot account for more than a fraction of the striking age trend in incidence of atheromatosis (Table 1). Whether this is simply a reflection of the biologic consequence of aging or a time-dose product of acquired "risk factors" is still unclear. Probably *both* altered tissue response and dosage of noxious influences are involved.

Families share more than genes and it is possible that those who sit and dine together may die together! It is clear that at any age in either sex some persons are distinctly more vulnerable than others to atherosclerotic disease outcomes depending on the number and intensity of "atherogenic" precursors in their makeup. Also, some persons manage to reach advanced age with little atherosclerosis suggesting that this "aging phenomenon" is not inevitable. We must learn what is responsible for this relative immunity and also those factors which, as regards atherosclerosis, make the potential victim of the process old beyond his years.

The ingredients of this "atherogenic profile" have been delineated from prospective epidemiologic studies in humans, at least in terms of the lethal clinical manifestations of atherosclerosis—coronary heart disease, brain infarction, occlusive peripheral arterial disease, and congestive heart failure. No essential factor—including lipid—has been identified as sufficient or absolutely necessary for the development of this

Table 1. *Risk Factors in Coronary Heart Disease. Linear Discriminant Function Coefficients (Standard Units)**

RISK FACTORS	COMBINED AGES	30–39	40–49	50–62
Men				
Age	.5934	.2394	.3334	.2370
Cholesterol	.4444	.9613	.3207	.3790
Systolic blood pressure	.3334	.3427	.1669	.3809
Relative weight	.1890	.1941	.3619	.1036
Hemoglobin	−.1050	.0313	−.0134	−.2206
Cigarettes smoked	.4192	.6823	.5084	.3004
ECG abnormality	.2626	.2685	.2556	.2197
Women				
Age	.6259	.7325		.2600
Cholesterol	.2844	.7322		.1207
Systolic blood pressure	.5556	.1947		.4776
Relative weight	.0975	.0751		.1481
Hemoglobin	.0392	−.0304		.0734
Cigarettes smoked	.0625	−.0731		.1262
ECG abnormality	.3048	.2234		.2526

**From* Kannel, W. B., and Gordon, T., eds.: The Framingham Study. An Epidemiological Investigation of Cardiovascular Disease. Section 27. Washington, D.C., U.S. Government Printing Office, 1971.

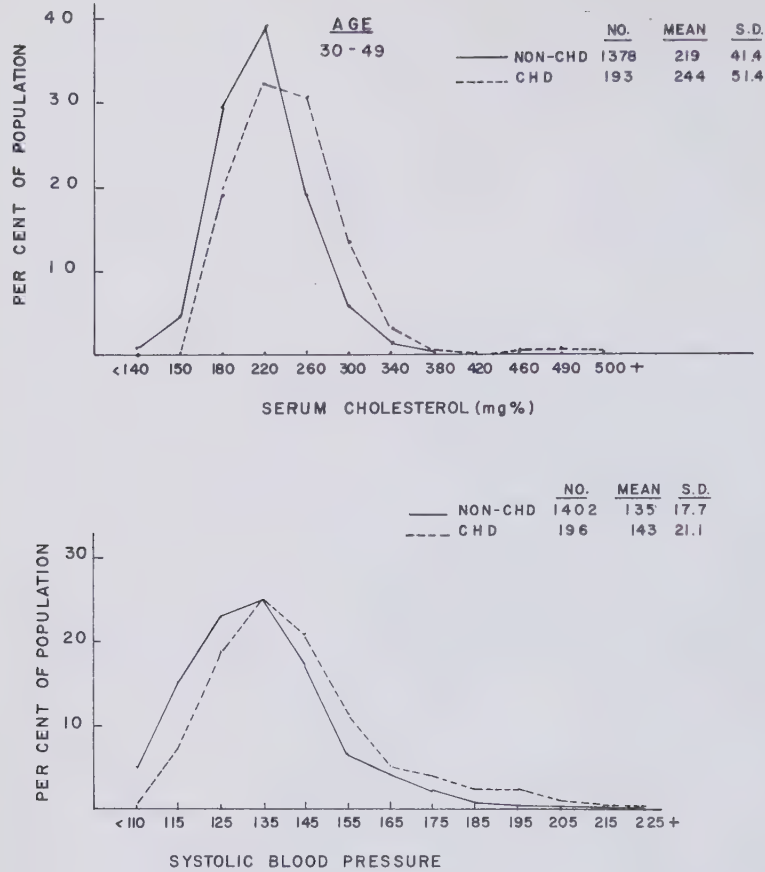

Figure 2. *Above,* Distribution of serum cholesterol in subjects free of coronary heart disease versus those developing coronary heart disease in 16 years. Men aged 30 to 62 at entry, Framingham Study. *Below,* Distribution of systolic blood pressure in subjects free of coronary heart disease versus those developing coronary heart disease in 16 years. Men aged 30 to 49 at entry, Framingham Study.

disease. Abnormalities predisposing to atherosclerosis and to its clinical manifestations are at this point more a matter of degree than kind. Multiple contributors rather than a single etiologic "agent" appeared to be playing a role.[7, 11, 13] Biologic factors involved in atherogenesis—such as blood lipids, blood pressure, and glucose tolerance—are graded characteristics of normal body constituents, continuously distributed with no discernible bimodality to denote where normal leaves off and "abnormal" begins.

Some physicians may find it difficult to cope with the concept of multiple, interrelated continuous variables contributing to a disease process. What is the level of these normal body constituents which initiates and sustains the process of atherogenesis? An examination of either blood lipids or blood pressure—the commonest and most potent atherogenic precursors in the make-up of the potential coronary victim—in a general population sample, comparing those who remain free of clinical disease

versus those who developed it, reveals Gaussian curves with long tails and no trace of bimodality (Fig. 2). There is a considerable overlap of values in diseased and well persons so that there is no value, however large or small, that lies distinctly in the distribution of one and not the other. Yet, risk of a coronary event is distinctly proportional to the antecedent level of either risk factor from the lowest to the highest values recorded in the population, the rate of increment accelerating around 200 mg. per 100 ml. for cholesterol (Fig. 3). Also, for blood pressure, risk is proportional to the level without any discernible critical "hypertensive" value where risk sharply rises. Even within the range generally conceded to be "normal" for these variables, risk varies over a fairly wide range (Fig. 4).

Thus, what is *typical* of apparently healthy persons in populations such as the United States may not in fact be "normal" or optimal at all. There is reason to believe, as judged by the values encountered in populations with low coronary mortality and little atherosclerosis at postmortem examination, that cholesterol values of Americans are far above optimal levels. Most Americans appear to have more than enough lipid to manufacture atheromata if given enough time. This may even be true for all human beings.

There apparently are pressures below which atheromata do not develop whatever the level of lipid in the blood—e.g., in the pulmonary arterial and venous circulation. Unfortunately such pressures within the systemic circulation are incompatible with life. Risk of all major atherosclerotic disease outcomes is proportional to the pressure in the systemic arterial circulation—systolic or diastolic, casual or basal—at all ages in both sexes. This is true even excluding persons with other risk attributes and, contrary to clinical folklore, there is no suggestion of a waning impact with advancing age (Fig. 4). However, its impact is profoundly influenced by the coexisting blood lipid value (Fig. 5).

The relation of blood lipid to clinical atherosclerotic events is also no

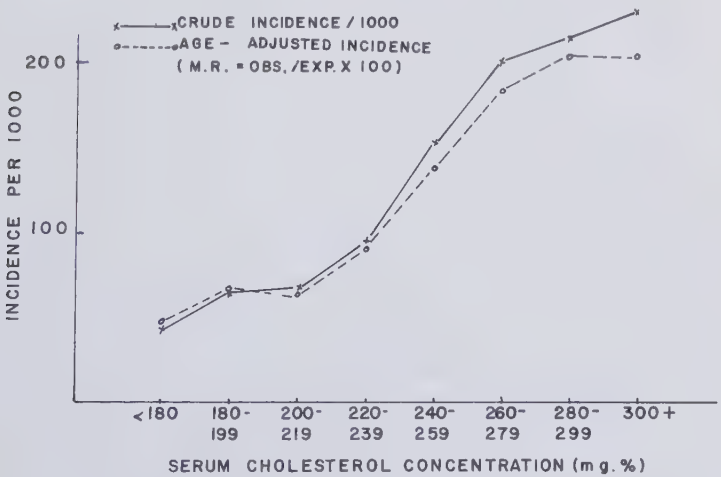

Figure 3. Risk of coronary heart disease (14 years) according to serum cholesterol concentration. Men aged 30 to 49 at entry, Framingham Study.

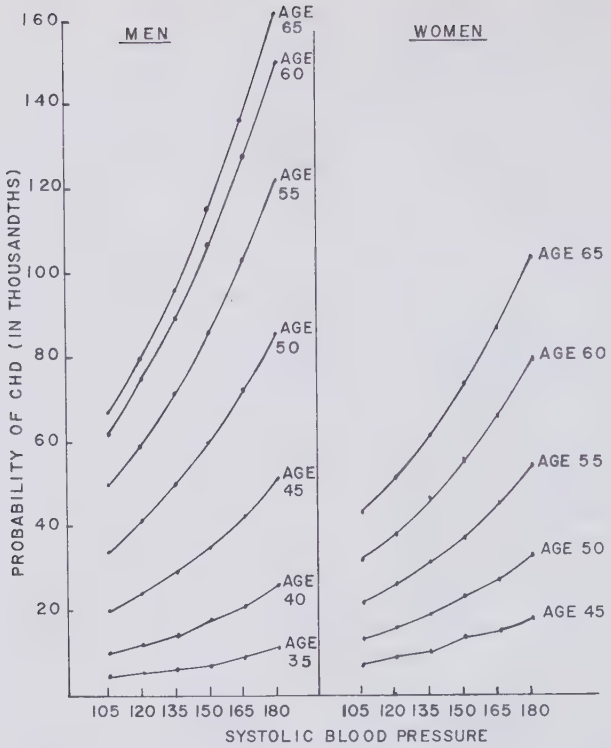

Figure 4. Probability of developing coronary heart disease in 8 years according to systolic blood pressure. Low risk persons aged 35 to 65, Framingham Study, 16 year follow-up. Persons with cholesterol 185, normal glucose tolerance, no left ventricular hypertrophy on electrocardiogram, nonsmoker. Source: Framingham Monograph No. 27.

accidental association by virtue of its correlation with other major risk factors. Taking other known powerful contributors into account, either categorically (Fig. 6) or using discriminant analysis (which adjusts for the actual value of associated variables as a group, Table 1), reveals a significant residual effect of cholesterol as well as blood pressure. If one examines the regression of coronary incidence on the major contributors to its occurrence, it becomes evident that overall the strongest of these factors is systolic blood pressure, followed in descending order by serum cholesterol, cigarette smoking, and blood sugar. The ranking is the same for women as for men with the exception of cigarette smoking which in women is quite weak. This is evident from a comparison of the size of computed regression coefficients suitably standardized for the different units and range of values of the variables under consideration (Table 2). It is also apparent from this table that both cholesterol and blood pressure contribute independently to risk of coronary events since the regression coefficients are only modestly reduced in the multivariate case which takes into account the effect of the other variables. Also, when adjustment is made for endogenous triglyceride carried in the pre-beta lipoprotein (S_f20–400 fraction) as well as other relevant factors, a risk gradient

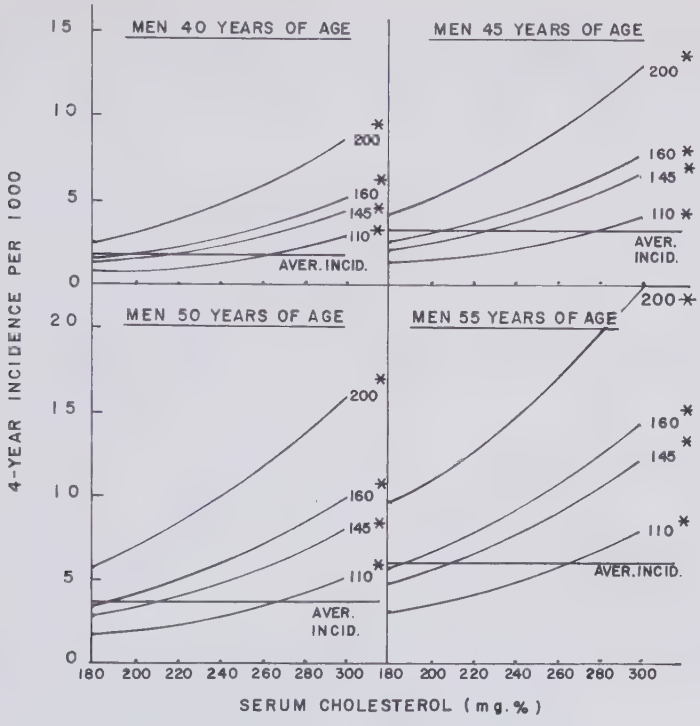

Figure 5. Four year incidence of coronary heart disease according to serum cholesterol concentration at specified levels of systolic blood pressure. Men aged 40 to 55, Framingham Study. Source: Framingham Monograph Section 23.

Table 2. *Average Regression Coefficients of Various Contributors to Incidence of Coronary Disease. 16 Year Follow-Up in Men and Women Aged 45 to 74**

	STANDARDIZED REGRESSION COEFFICIENTS			
	Men		Women	
	Univariate	Multivariate	Univariate	Multivariate
Systolic blood pressure	.340	.264	.477	.408
Serum cholesterol	.257	.226	.296	.267
ECG-LVH	.234	.173	.262	.161
Cigarettes	.186	.246	–.024†	.032†
Glucose Intolerance	.172	.153	.124	.074†

**From* Kannel, W. B., and Gordon, T., eds.: The Framingham Study. An Epidemiological Investigation of Cardiovascular Disease. Section 27. Washington, D.C., U.S. Government Printing office, 1971.

†Slope of CHD incidence on the variable is not significant at the 5 per cent level.

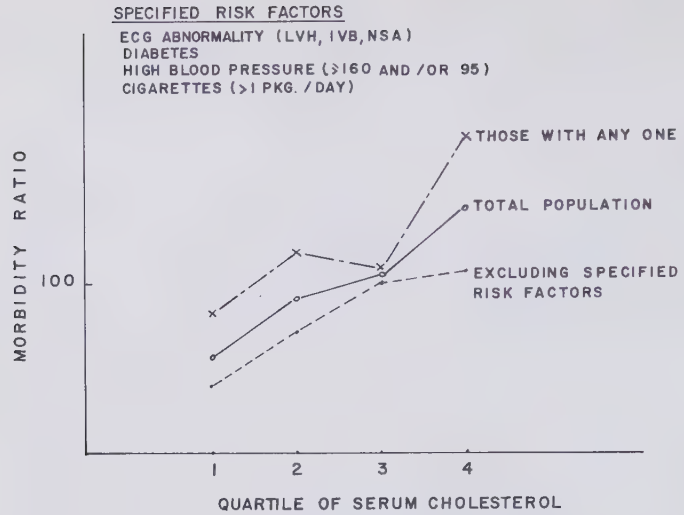

Figure 6. Risk of coronary heart disease (16 years) according to serum cholesterol concentration, excluding other factors. Men aged 30 to 62 at entry, Framingham Study.

still persists which is proportional to the serum cholesterol value (Fig. 7). The converse is not true. Evidently, as applied to the general population, serum lipid profiles are more useful for determining the cause of an elevated blood cholesterol and the best means to reduce it than for estimating the risk of coronary attacks.

Taking age and sex into account and assuming that the intrinsic architecture of the arterial vasculature is randomly distributed, serum lipids (cholesterol in particular), blood pressure, and carbohydrate toler-

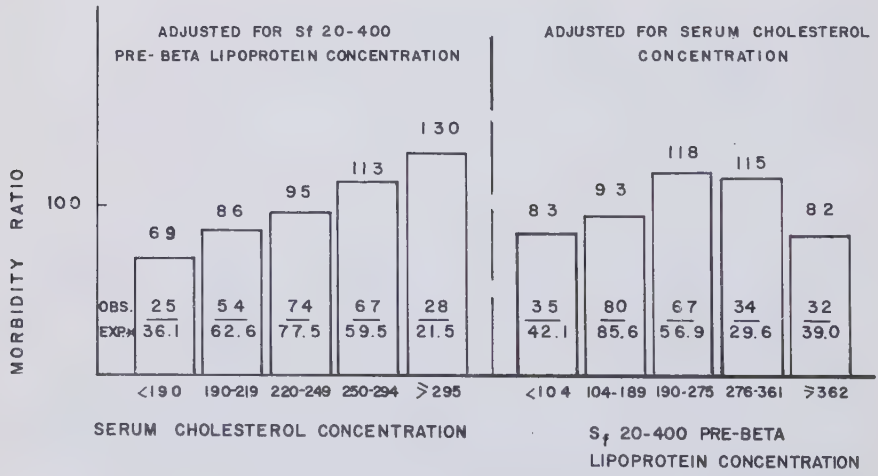

Figure 7. Risk of coronary heart disease (14 years) according to serum lipid, adjusted for associated variables. Men aged 38 to 69 years, Framingham Study. *Exp, Expected number of events obtained from "risk function" derived from: blood pressure, number of cigarettes, uric acid, glucose, relative weight, and other serum lipid under consideration.

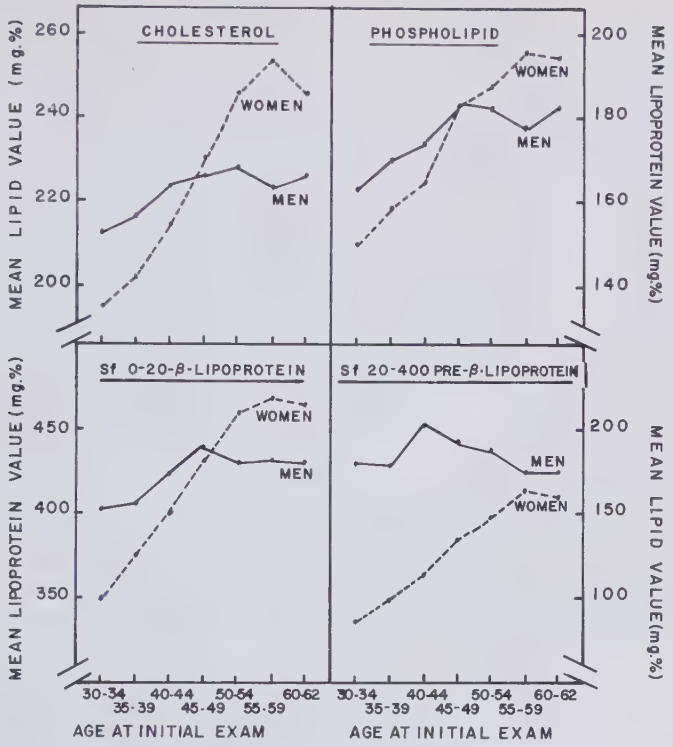

Figure 8. Mean value of serum lipids by age and sex at initial examination. Men and women aged 30 to 62 at entry, Framingham Study.

ance appear to be the chief determinants of the rate of atherogenesis as it is clinically expressed. An examination of age-sex trends in blood lipid (Fig. 8) and in blood pressure (Fig. 9) reveals an intriguing similarity to that in clinical atherosclerosis, where the relative immunity in women is lost with advancing age (Fig. 10). This raises the possibility that the closing gap in incidence in the sexes with advancing age derives to some extent from fact that pressures and lipid values in women rise to meet and finally exceed those in men. Epidemiologic studies such as the Framingham study can only provide clues to pathogenesis and not definitive answers. However, there is a considerable body of evidence to connect the blood cholesterol content with the development of atherosclerosis. The strengths and weaknesses of this information have been discussed at some length.[1,2]

That an association exists between cholesterol and atherosclerosis is incontrovertible. That it is a *causal* association is more difficult to prove. We are currently in the position of having to prove guilt by association. An association is more likely to be "causal" if it precedes the disease by an appropriate incubation period, if it is strong, and, most important, if it makes sense. The association between cholesterol and atherosclerosis appears to meet all these criteria.

Prospective data show that blood cholesterol values long in advance

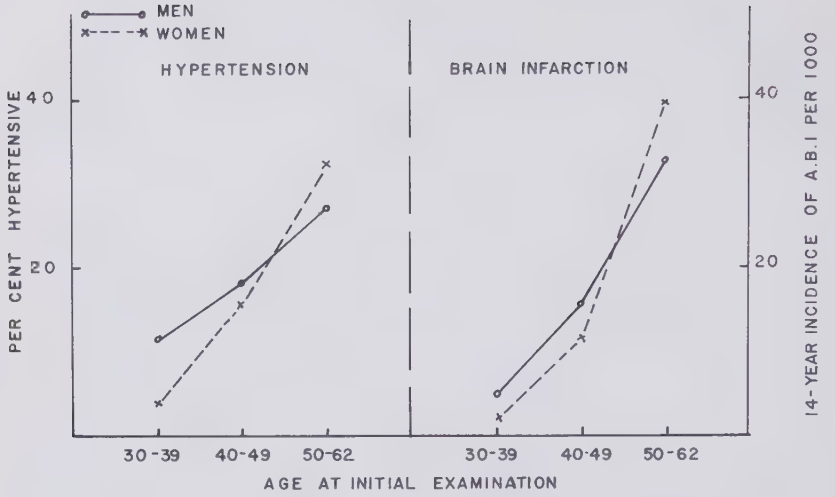

Figure 9. Prevalence of hypertension and incidence of atherothrombotic brain infarction by age and sex. Men and women aged 30 to 62 at entry, Framingham Study.

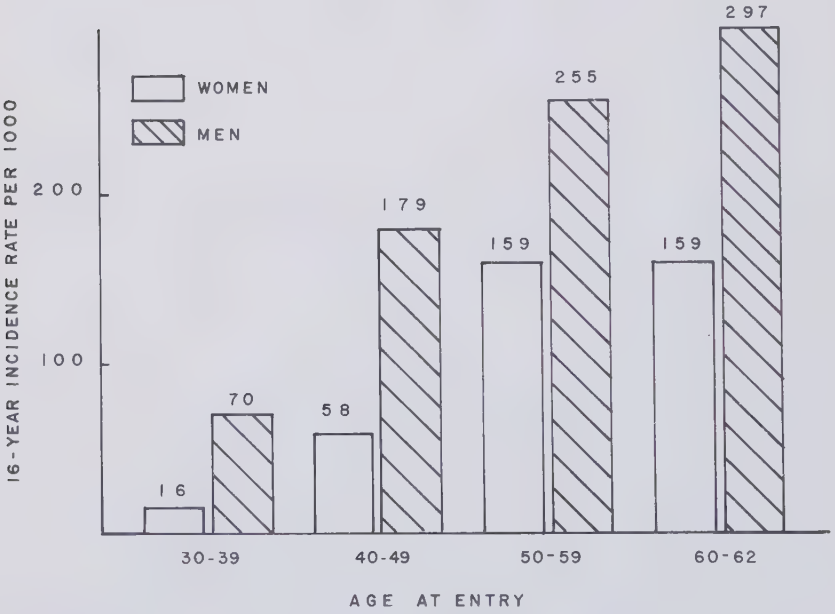

Figure 10. 16-Year incidence of coronary heart disease in men and women aged 30 to 62 at entry, Framingham Study.

of the disease are strongly related to the rate of development of its clinical manifestations consistent with the known insidious evolution of atherosclerosis. The risk varies in relation to the associated blood pressure, consistent with the filtration or perfusion hypothesis. Animal experiments in a variety of species have demonstrated unequivocally that lipid-induced atherogenesis is markedly accelerated by also producing hypertension.[8, 10, 14, 18] While the perfusion hypothesis is a gross oversimplification of this complex process, the data from epidemiologic clinical and postmortem studies in man are quite consistent with it. It is likely that an alteration in the level or handling of blood lipids, augmented by the level of the blood pressure, is in most instances the final common pathway through which the multiple interrelated contributors to atherosclerosis operate. To argue that these are innocuous, nonsequitor concomitants of some more basic process seems overly iconoclastic in the face of the evidence.

That cholesterol is somehow associated with the atherosclerotic process and its evil consequences is incontrovertible. Whether it is etiologic in the sense of an essential factor or even the initiator of the process given the right substrate of circumstances is conjectural at this point, but not likely. Cholesterol seems to be the thread running through the web of circumstances culminating in a clinical atherosclerotic event. The conclusion that blood lipid (cholesterol in particular) makes some type of major contribution to the process of atherosclerosis and its lethal sequelae seems inescapable. The chain of evidence is too binding to be cast aside. Diseases associated with hypercholesterolemia are also associated with premature atherosclerosis. Persons with inborn errors of cholesterol metabolism show extremely precocious development of atherosclerotic disease. Persons with high cholesterol levels in epidemiologic study populations have been observed to develop coronary heart disease with greater frequency than those with lower values, the risk being proportional to the degree of elevation of blood cholesterol. Countries with high average cholesterol values among their inhabitants report high coronary death rates, those with low values report low rates. Atherosclerotic deposits are usually loaded with cholesterol and other lipids and the movement of cholesterol from the blood into deposits has been demonstrated. Inducing high cholesterol values in animals produces atherosclerotic deposits that can be made to regress by lowering blood cholesterol.

There are problems with all of this evidence,[1, 2] but efforts are being made to further refine it, and thus far results have continued to confirm the findings in evermore convincing fashion.[3, 10, 19] However, further clarification is still needed. When or if the final link in the chain of evidence is forged, demonstrating that in man substantial lowering of cholesterol in fact reduces coronary morbidity and mortality in a controlled field trial, the need for this evidence will become less acute. Such evidence is beginning to accumulate.[17] The problem is really largely a question of degree. The contention that the deposition of cholesterol is only incidental to its availability in the circulation and that atheromata would probably form even in persons with low lipid values is valid.[1, 2] However, the simple fact is that in animals and in man the process is unequivocally accelerated in proportion to the blood lipid level, and in persons with runaway choles-

terol synthesis resulting from inborn errors of metabolism extremely precocious atherosclerosis occurs which has been known to strike down whole families of these unfortunates early in life, sometimes in the teens. Further, while the fibrotic vascular lesions of atherosclerosis may develop in the face of seemingly innocuous lipid levels and the lesions may contain only modest amounts of lipid, possibly formed in situ, these are generally not the lesions that occlude vessels and precipitate thrombi. It is the fatty atheromatous abscess that is especially likely to precipitate such vascular catastrophies.

The determinants of the generally high lipid values in the United States, the biologically optimal range of values, the details of its regulation, and the pathogenesis of the atherosclerotic lesion, however, require further clarification. The reasons for incriminating diet as one of the chief determinants of lipid levels in a population are substantial but somewhat confusing.

It is paradoxical that in free-living affluent populations no one has convincingly demonstrated a difference in nutrient composition of the diet between persons who develop coronary heart disease and those who do not. Nor has there been a demonstration, *within* such populations, of a connection between the nutrient content of the diet and serum cholesterol values from one person to the next. Yet, there is much to suggest that the nutrient composition of the diet may be an important if not the key determinant of the general level of cholesterol in a population.

The evidence linking blood cholesterol content to the nutrient composition of the diet is too substantial to dismiss. An impressive amount of evidence has accumulated from epidemiologic studies, animal investigation and manipulative studies in humans to incriminate the saturated fat, cholesterol and refined carbohydrate in the diet as promoting hyperlipidemia and being atherogenic. Areas in which the population exhibits high cholesterol values characteristically have diets different in composition and calories from those where low values are usual. Migrants from low to high cholesterol areas are found to have higher cholesterol values and to have changed, among other things, their dietary pattern. Manipulation of the diet can alter serum cholesterol values in a predictable fashion in humans, and in animals can produce atherosclerotic deposits or cause established lesions to regress.[3] Both have even been shown to occur in monkeys on American table diets.[19]

Again, fault can be found with each one of these pieces of evidence but they too paint a rather consistent picture. Critics of the animal experiments correctly point out the "unnatural" dietary conditions employed to induce atherosclerosis, but the same indictment must be made concerning the unnaturalness of the zoo environment when findings in such animals are cited to refute animal experiments purporting to show diet-induced atherosclerosis.[1, 2] Also, there is reason to believe that the diet of the average American is far from "natural." Over the past century some rather profound changes have been made in the saturated fat, cholesterol, refined sugar, and salt content of the diet. It is highly unlikely that if man were returned to his "natural" primitive predatory state that he could obtain this much fat and salt in his diet. It takes a highly organized society to sustain this rich a diet without expending considerable calories of energy to acquire the foodstuffs.

The absence of a correlation between what people say they eat and their blood cholesterol values within free-living affluent populations on uniformly high intakes of all the incriminated nutrients has been taken by some to mean that diet plays no role in the evolution of atherosclerosis or its serum lipid precursors. However, it may be that the association does not reveal itself to casual observation, and diet may still constitute the chief factor determining the average blood cholesterol value of a population. Failure to demonstrate an association between diet and serum cholesterol values from person to persons *within* an affluent population may stem from the fact that there are not enough people who habitually consume the kind of diet characteristic of low cholesterol areas of the world, or that which must be fed in order to lower lipids on a metabolic ward. Evidently, at the high nutrient intakes characteristic of affluent populations, the variation in cholesterol values found *within* the population depends on factors other than the degree of overload of the incriminated nutrients. Good possibilities are innate ability to cope with the nutrient overload, energy balance, and state of health.

In free-living affluent populations there may simply not be a biologically correct range of nutrient intakes to allow a demonstration of the influence of diet on blood lipids *within* the population. For example, Connor has shown that in the range of dietary cholesterol intakes between 0 and 400 mg. per day, blood cholesterol levels achieved are proportional to intake. Beyond this range, there is little discernible association between the two.[4] The bulk of persons in affluent populations are above this range in their cholesterol intake and may also be above the threshold for saturated fat and refined carbohydrate.

While studies within free-living populations have not shown much relation of dietary practices to interindividual lipid values, there are some studies carried out in captive populations such as mental hospitals which have conclusively shown that when subjects actually adhere to diets low in cholesterol and saturated fat, substantial decreases in serum cholesterol occur and then revert on return to house diet.[17]

Also, the problem appears to be more complex than originally conceived to be. Recent evidence suggests that some persons with high cholesterol values may be more sensitive to the carbohydrate overload of their diet, while others are unable to cope with the saturated fat and cholesterol. They may be distinguishable by their lipoprotein pattern, serum triglyceride values, glucose tolerance, and serum turbidity. Such factors have not to date been adequately taken into account in diet studies. This may also explain why physicians attempting to lower serum cholesterol values by dietary manipulation are sometimes disappointed with the result. They may, in some instances, have failed to ascertain the type of hypercholesterolemia present and did not tailor the dietary modification to the lipoprotein pattern.

However, whether one subscribes to the hypothesis that diet is the chief determinant of acquired hypercholesterolemia or not, the evidence incriminating hypercholesterolemia in atherogenesis is too formidable to brush aside. Much remains to be learned. Perhaps the partition of cholesterol among the various lipoprotein fractions determines its atherogenicity or the way in which it becomes elevated is responsible, but one thing

Table 3. *Probability* of Developing Coronary Heart Disease in 8 Years by Sex, Age, Systolic Blood Pressure, Cholesterol, Left Ventricular Hypertrophy by EKG, Cigarette Smoking and Glucose Intolerance. The Framingham Study. 16-Year Follow-Up***

45 YEAR OLD MAN*,*

	DOES NOT SMOKE CIGARETTES							SMOKES CIGARETTES						
	LVH EKG NEGATIVE													
	SBP	105	120	135	150	165	180	SBP	105	120	135	150	165	180
	CHOL							CHOL						
	185	20	24	29	35	42	51	185	32	39	46	56	67	81
Glucose	210	25	30	36	44	53	64	210	40	48	58	69	83	99
intolerance	235	31	38	45	55	66	79	235	50	60	72	85	103	122
absent	260	39	47	56	68	81	97	260	62	74	89	105	126	149
	285	48	58	70	84	100	119	285	76	92	109	130	153	181
	310	60	72	87	104	123	146	310	94	113	134	158	186	217
	SBP	105	120	135	150	165	180	SBP	105	120	135	150	165	180
	CHOL							CHOL						
	185	25	30	36	44	53	64	185	40	48	58	69	83	99
Glucose	210	31	38	45	55	66	79	210	50	60	72	86	102	122
intolerance	235	39	47	56	68	81	97	235	62	74	89	106	126	149
present	260	48	58	70	84	100	119	260	76	91	109	130	153	181
	285	60	72	87	103	123	146	285	94	112	134	158	186	217
	310	75	89	107	127	150	177	310	116	138	163	191	223	259

LVH-EKG POSITIVE

	CHOL \ SBP	105	120	135	150	165	180
Glucose intolerance absent	185	41	50	60	72	86	102
	210	51	62	74	89	106	126
	235	64	76	91	109	130	153
	260	79	94	112	134	158	186
	285	97	116	138	163	191	223
	310	120	142	167	196	229	266
Glucose intolerance present	185	51	62	74	88	106	126
	210	64	76	91	109	129	153
	235	79	94	112	133	158	186
	260	97	116	137	162	191	223
	285	119	142	167	196	229	265
	310	146	172	202	235	272	313

CHOL \ SBP	105	120	135	150	165	180
185	65	78	93	111	132	157
210	81	95	115	136	161	189
235	100	118	141	166	195	227
260	122	145	171	200	234	270
285	149	176	206	240	277	318
310	181	212	246	284	326	370
CHOL \ SBP	105	120	135	150	165	180
185	81	96	115	136	161	189
210	99	118	140	166	195	227
235	122	145	171	200	233	270
260	149	176	206	240	277	318
285	181	211	246	284	325	370
310	217	252	291	333	378	425

*Probability is shown in thousandths.

**From Kannel, W. B., and Gordon, T., eds.: The Framingham Study. An Epidemiological Investigation of Cardiovascular Disease. Section 27. Washington, D.C., U.S. Government Printing Office, 1971.

***Framingham men aged 45 years have an average systolic blood pressure of 131 mm. hg and an average serum CHOL of 235 mg. per 100 ml. 67 per cent smoke cigarettes, 1.3 per cent have definitive LVH and EKG and 3.8 per cent have glucose intolerance. At these average values the probability of developing coronary heart disease in 8 years is 60/1000.

is clear, it is somehow intimately involved in the process of atherosclerosis.

While there are problems with some of the observations linking cholesterol to atherogenesis and some of the details are a bit hazy, there is too much that remains to be explained away. True, not everything that looks like a goat is in fact a goat. But, when it also smells, tastes, feels, and sounds like one, it seems reasonable to start thinking in terms of goat! There is ample precedent for the concept that a disease can be prevented long in advance of the elucidation of its etiology, provided one can determine the chain of events in its evolution within a population. By interrupting this chain the disease can often be prevented. Cholesterol appears to be a distinct link in this chain but at present a multifactorial approach, modifying as many of the precursors as possible, would appear to offer the greatest hope of success in avoiding atherosclerotic disease. To this end a coronary profile can be arrived at for the asymptomatic patient using ordinary office procedures and a simple laboratory test. From the determination of a blood cholesterol, blood pressure, glucose tolerance, cigarette habit, and electrocardiographic status with respect to left ventricular hypertrophy (or intraventricular block or nonspecific S-T and T-wave changes), the probability of a coronary attack can be estimated over a wide range (Table 3)—in this case 20-fold. It can also be seen that a 260 mg. cholesterol value may be associated with only a 4 per cent probability of a coronary event in 8 years if all other factors are favorable, or with an ominous 32 per cent probability if all others are not. Thus cholesterol, like any other contributor to coronary mortality, is best considered one ingredient of a coronary risk profile. Its impact is profoundly influenced by associated risk factors.

Evidence available from the Framingham study strongly suggests that there is a common set of precursors for all the major cardiovascular atherosclerotic diseases, whether manifest in the heart, brain, or limbs. The major risk factors for coronary heart disease taken jointly will predict brain infarction and occlusive peripheral arterial disease at least as well as coronary heart disease. This provides additional evidence that these cardiovascular diseases arise from a common substrate and very likely share a common cause. It also strongly suggests that successful prophylactic intervention against one of these atherosclerotic diseases, if successful, might well carry the considerable bonus of a reduced incidence of the others as well. And a prophylactic approach to the atherosclerotic diseases is imperative if substantial inroads against the appalling annual toll of mortality they exact is to be made. The bulk of coronary mortality occurs suddenly and unexpectedly out of reach of medical care no matter how sophisticated it is or may become.

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The Role of Trace Elements in Cardiovascular Diseases

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Certain trace elements are essential for the life or health of mammals—as well as of other living things. Vanadium, chromium, manganese, iron, cobalt, copper, zinc, and molybdenum are metals having a definitive role in mammalian metabolism or having demonstrated effects on growth or survival. Selenium, fluorine, and iodine are nonmetals with biologic effects. In addition, strontium may play a role in the formation of bones and teeth.

So basic are the functions of many of these elements, especially the metals, that it would not be surprising to find alterations in their concentrations in a large number of conditions involving malfunction or destruction of tissue, with secondary changes in tissue components. Furthermore, because metallic cofactors of enzymes or activators of enzyme systems perform basic metabolic reactions, it would not be surprising to discover that certain chronic diseases result from tissue deficiency of one or another trace element.

The evolution of industry based on the use of metals which culminated in the Industrial Revolution had as one of its side effects contamination of the globe with certain metals found naturally in low concentrations. Some of these metals are innately toxic, a quality not found in low concentrations of the elements essential for life or health: cadmium, lead, mercury, antimony, beryllium. Living things have evolved in the presence of very low concentrations of these toxic elements, and the need for detoxifying systems has been relatively unnecessary—until the present. Now, as best can be ascertained, the body burdens of industrialized urban man are elevated with respect to three elements: lead, cadmium, and arsenic, certainly the result of modern industrial practices. Therefore, it would not be surprising if some chronic disease resulted from metabolic breakdown coming from accumulation of an abnormal toxic trace element during a lifetime.

The common chronic diseases of our civilization which are unusual

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in some other people are atherosclerosis, hypertension, arthritis, cancer, diabetes, and cirrhosis of the liver, which make up the leading causes of death and disability. Some of these disorders are at least partly affected by dietary factors. Therefore, a search must be made on the relation of trace elements—deficiencies of essential ones and excesses of toxic ones—to common chronic diseases.

A great deal of investigative work has been done on these problems. In fact, the World Health Organization is now conducting a large survey on cardiovascular disease and trace elements in tissues and in the environment.[18] Enough evidence, both indirect and direct, has now accumulated to involve trace elements as causal factors of two cardiovascular diseases, atherosclerosis and hypertension.

ATHEROSCLEROSIS

Background

The body burden of chromium in Americans was low, many tissues being deficient, and levels declining with age.[34, 44] This finding contrasted with body burdens of Africans, Near Easterners, and Orientals, which were much higher. In fact, tissues of Thai had more chromium than any other group, and the incidence of aortic atherosclerosis was very low.[28] Furthermore, there were few atherosclerotic complications, such as myocardial infarctions or cerebral vascular accidents. High tissue levels of chromium were generally found in areas where there was little atherosclerosis, but in advanced countries levels tended to be low—such as in England,[48] where it was seldom detected.

The disorder of carbohydrate and lipid metabolism which causes serum cholesterol to increase with age and which produces lipid deposits in sub-intimal areas of the arteries is characterized by (a) elevated blood lipid levels and (b) abnormal tolerance for glucose. Consequences of these lipid deposits plus clotting of blood results in thrombosis of coronary and cerebral arteries and sometimes of femoral arteries, with resultant death or disability. In myocardial infarction or coronary thrombosis without infarction, the atherosclerotic process is believed to be enhanced by the frequent presence of hypertension, another disease.

It is not the purpose of this discussion to consider effects, but only causes, and to separate diseases which often occur together. The frequent coexistence of mild or moderate hypertension and coronary accident, however, obscures much epidemiologic data and leads to erroneous interpretations based on them. Therefore, we will consider atherosclerosis per se, whether it involves disease or death, in brain, heart or extremities, and treat it as one disease.

Epidemiologic Data—the Water Factor

The death rate from coronary heart disease has long been shown to vary significantly from one area to another. This variation was discovered to be inversely related to some quality of drinking water associated with its hardness.[30-32, 48] The relation held not only in countries such as Great Britain,[21] Sweden,[3] and Canada,[1] but even in small countries such as the

Netherlands,[18] and in states such as Washington[18] (but not in Oklahoma); but not in Japan, where the first observations were made.[16] There, cerebral vascular accident is the first cause of death, most cases being due to hemorrhage, and the relationship was demonstrated between this disorder and the acidity of river water, directly. Almost all Japanese waters are soft. At this point, the case for hypertension being related to water quality was as good or better than for coronary disease to be so related. At any rate, some geochemical factor in water, presumably elemental, was involved in cardiovascular deaths.

All reports, except those of Kobayashi[16] and Schroeder[30, 31] considered coronary heart disease and factors in water. It was not until Masironi examined the problem that a dichotomy between hypertensive heart disease and coronary heart disease appeared in the data, to the exclusion of the latter.[17] Masironi went back to Kobayashi's original thesis, that river water was related to death rates, and found significant correlations of a number of elements in water and regional death rates from hypertensive, but not coronary, heart disease.

Death rates in white males aged 45 to 64 years in 42 states were inversely correlated with the following trace elements and qualities of water: hardness, α-radioactivity, cobalt, nickel, chromium, molybdenum, vanadium, zinc, manganese, fluorine, and boron; these correlations were significant at the 0.05 to 0.01 level of confidence. In addition, death rates were inversely related to the concentrations of the toxic trace elements antimony, bismuth, cadmium, lead, silver, tin, at the same level of confidence, but insignificantly to barium, beryllium, iron and copper.

The results of all of these surveys were to leave us with a variety of elements related to death rates from hypertensive heart disease, without a single outstanding one suspected of being causal (Table 1).

When one examines the data with a view to deciding whether or not an element occurs in water in sufficient amounts to negate a food deficiency of the element, one is left with the conclusion that, with few exceptions, water usually supplies minor and negligible increments to the total dietary intake of trace elements. These relationships are given in Table 2. The median values show that water provides less than 7 per cent of the essential elements, fluorine being an exception. The extreme values—for hard water—indicate significant increments of magnesium, chromium, manganese, and molybdenum, each of which has been implicated in cardiovascular disorders. Such large increments must be rare.

Of the non-essential elements, water provides several times more silicon than food, but silicon is not readily absorbed by the intestine. Water also provides sizable increments of barium, strontium, boron, titanium and uranium in hard water areas. These elements have very low orders of toxicity. Some cadmium, which is toxic and cumulative, is provided by water, especially soft water running through pipes. Very toxic metals, such as bismuth, beryllium, and antimony, are present in water only in traces.

Therefore, of these many studies, we can implicate marginal intakes in soft water areas and luxus intakes in hard water areas of magnesium, chromium, manganese, and molybdenum, and the reverse situation for cadmium. The water factor offers indirect evidence that a trace metal or

Table 1. *Correlation Coefficients* (r) *of Some Waterborne Trace Elements and Death Rates from Hypertensive Heart Disease and Atherosclerotic Heart Disease (United States data, white males aged 45–64 years)*

ELEMENT	RIVER WATER, HYPERTENSIVE HEART DISEASE		MUNICIPAL WATER, ATHEROSCLEROTIC HEART DISEASE	
	r	*P*	*r*	*P*
Potassium	–	–	–0.48	<0.0005
Magnesium	–	–	–0.40	<0.0005
Hardness	0.44	<0.01	–0.41	<0.0005
Silicon	–	–	–0.34	<0.0005
Sodium	–	–	–0.27	<0.01
Calcium	–	–	–0.23	<0.02
Vanadium	–0.41	<0.05	–0.34	<0.0005
Barium	–0.26	–	–0.34	<0.0005
Copper	+0.11	–	+0.29	<0.005
Strontium	–	–	–0.29	<0.005
Lithium	–	–	–0.28	<0.005
Manganese	–0.35	<0.05	+0.26	<0.01
α-radioactivity	–0.42	<0.01		
β-radioactivity	–0.52	<0.001	–0.21	<0.025
Boron	–0.34	<0.05		
Lead	–0.46	<0.01		
Nickel	–0.36	<0.05		
Molybdenum	–0.36	<0.05		

Data from Masironi[17] and Schroeder.[30]
Essential elements in italics.

metals affect human death rates from hypertensive heart disease and so indirectly from arteriosclerotic heart disease.

For many years we have puzzled over the question as to whether hard water was protective or soft water lethal in hypertensive heart disease.[30, 31] The conclusion that soft water has some detrimental quality appears the logical one. As soft water is usually acid and usually corrosive to pipes, some metal coming from water pipes is probably involved. The only metal with the ability to cause hypertension in rats[26] shown to be dissolved by soft water from pipes[45] is cadmium. Therefore, cadmium is suggested as the water factor, entering the body via water from galvanized pipes and solders.[35]

Atherosclerosis, Experimental

Although many people have investigated atherosclerosis in animals, both laboratory and zoo, the approach has generally been on the basis of exercise, lipids, or carbohydrates. Wild animals seldom show the disease, but animals in captivity often do.

A diet designed for rats, of whole rye flour, dry skim milk, and corn oil, was found fortuitively to be deficient in chromium and to cause aortic plaques, elevated serum cholesterol and elevated fasting blood sugar.[27, 37] In other words, this diet reproduced in rats the human atherosclerosis

Table 2. *Increment of Bulk and Trace Elements in Water to Total Dietary Intakes*

ELEMENTS	WATER		FOOD	PER CENT FROM WATER	
	Median mg.	Maximum mg.	mg.	Median	Maximum
Essential					
Calcium	52	290	800	6.5	36.3
Magnesium	12.5	240	210	5.9	114.3
Sodium	24	396	4,400	0.5	9.0
Potassium	3.2	60	3,300	0.09	1.8
Vanadium	<0.008	0.14	2	0.6	
Chromium	0.001	0.07	0.1	1.0	70.0
Manganese	0.01	2.2	3	0.3	73.3
Iron	0.09	3.4	15	0.6	22.7
Cobalt	0.006	0.01	0.3	2.0	3.3
Nickel*	0.005	0.07	0.4	1.3	17.5
Copper	0.02	0.5	2.5	0.8	20.0
Zinc	0.5	2.1	13	3.8	16.2
Selenium	<0.02	–	0.15	<13.3	–
Fluorine	0.4	14	1.8	22.2	777.8
Molybdenum	0.003	0.14	0.34	0.9	41.2
Non-Essential					
Silicon	14.2	144	3.5	405.7	4100
Aluminum	0.1	3.0	45	0.2	6.7
Barium	0.09	0.76	1.24	7.3	61.3
Strontium	0.22	2.4	2	11.0	120.0
Boron	0.06	1.2	1.0	6.0	120.0
Bismuth	trace		0.002	–	–
Beryllium	trace		0.00001	–	–
Antimony	trace		<1.0	–	–
Lead	0.007	0.12	0.41	1.7	29.3
Lithium	0.004	0.34	~2.0	0.2	17.0
Silver	0.005	0.014	0.07	7.1	20.0
Tin	0.002	0.005	4.0	0.05	0.1
Titanium	<0.003	0.1	0.3	0.1	33.3
Uranium	0.0003	0.5	1.4	0.02	35.7
Cadmium	0.005	0.02	0.07	7.1	28.6

Data from Durfor and Becker,[6] Howell,[13] and Schroeder[41] at 2 liters per day.
*Nickel is possibly essential for mammals, but unproven.

syndrome.[44] Diets even lower in chromium, using refined white sugar as the major carbohydrate, also produced the syndrome, which was prevented by substitution of raw or dark brown sugar which contained adequate chromium.[17, 40] To date, attempts to reverse the disease, once established, have not been made.

Human Counterpart by Analyses

Persons in the United States and abroad dying of coronary heart disease had virtually no chromium in their aortas, whereas those dying of accidents or other diseases had aortic chromium[44] (Table 3). There were virtually no differences in hepatic chromium in the two groups. In general, tissues of United States subjects were low or deficient in chromium,

Table 3. *Chromium in Aortas of Subjects Dying from Atherosclerotic Heart Disease, Other Cardiovascular Diseases, and Accidents*

LOCATION	NO. OF CASES	AORTIC CHROMIUM μg/g	PREVALENCE PER CENT	P
San Francisco				
Atherosclerotic heart disease	15	0.05 ± 0.009	13.3	
Atherosclerotic heart disease moderate	3	0.03 ± 0.003	0	–
Accidents	10	0.23 ± 0.076	80	<0.005
United States–9 cities				
Atherosclerotic heart disease	13	0.05 ± 0.088	46.2	–
Other cardiovascular disease	15	0.20 ± 0.090	60	–
Accidents	103	0.26 ± 0.067	87.4	<0.005
Africa				
Cardiovascular disease	2	0.12 ± 0.026	100	–
Other	11	0.19 ± 0.025	90.9	<0.025
Mid-East				
Cardiovascular disease	3	0.22 ± 0.084	66.7	–
Other	11	1.28 ± 0.831	100	–
Far East				
Atherosclerotic heart disease	5	0.25 ± 0.132	100	–
Cardiovascular disease	20	0.31 ± 0.073	85	–
Accidents	8	0.97 ± 0.532	100	–

Data from Schroeder et al.[44]

compared to tissues of foreign subjects.[34, 44] These differences were especially marked in the case of aortic chromium (Table 4). In all five areas of the world, there was more aortic chromium, and it was more prevalent in subjects dying of accident or other causes than in subjects dying of atherosclerotic heart disease. Aortic chromium in subjects dying of other cardiovascular or cerebrovascular diseases was intermediate in value.

Causes of Chromium Deficiency

The exact causes of aortic chromium deficiency are not known, although relative body deficiency is probably the result of two factors. Natural chromium occurs as an organic complex called the glucose tolerance factor, which is stable, readily absorbed by the intestine, and passes the placental barrier. It is present especially in wheat germ, bran, and probably molasses, as well as in brewer's yeast. Chromic salts or simple complexes olate (form long, hexa-aquo molecules) in alkaline media, are absorbed by the intestine only to a point of 0.5 per cent,[5] and do not pass

Table 4. *Aortic Chromium from Various Geographic Areas*

	NO. CASES	MEAN ± SEM μg/g ash
United States	64*	1.9
9 cities	150	4.4 ± 0.5
San Francisco	27	2.6 ± 1.1
Honolulu	12	14 ± 4.3
Anchorage	2	13 ± 9.7
Far East	35*	15†
Japan	28	15 ± 2.9
Taipei	10	26 ± 10
Manila	10	37 ± 11
Bangkok	10	44 ± 24
Hongkong	10	7.6 ± 1.9
Africa	13*	5.5
Caucasoid	13	4.3 ± 1.4
Negroid	41	7.5 ± 2.8
Addis Ababa	5	3.7 ± 1.8
Lagos	17	3.7 ± 1.1
Cairo	8	6.0 ± 2.1
Welkom	5	25 ± 6.5
Bern, Switzerland	9*	30 ± 23
India	9*	11†
Delhi	8	6.0 ± 1.9
Lucknow	4	22 ± 11
Bombay	8	71 ± 55

Data from Schroeder et al.[44]
*Males 20 to 59 years old, only.
†Differs from United States value, $P < 0.001$

the placental barrier.[19] Refining of wheat to make white flour, of sugar to make white sugar, and of fats to make white or yellow fats and oils removes most of the chromium available for the body (Table 5). The use of much chromium-poor glucose or sucrose would add little to body stores, and would probably mobilize chromium from body stores into the blood,[7] from whence part is excreted in the urine, producing a net loss. Whereas chromium-rich sugars would have the same effect, the net result would be a favorable chromium balance. The rat requires the

Table 5. *Losses of Chromium and Manganese in Common Foods (wet weight)*

	REFINED		UNREFINED	
FOOD	Cr, μg/g	Mn, μg/g	Cr, μg/g	Mn, μg/g
Wheat	0.03	6.5	0.05	46.0
Sugar	0.0–0.11	0.13	0.19–0.42	1.75
Animal fats	0.07–0.10	0.98	0.21–0.23	–
Vegetable oils	0.03–0.07	1.47	0.23	2.52
Hospital diet	0.056–0.066	0.96	–	3.0

Data from Schroeder[38, 44]

Table 6. *Significant Differences in Elemental Content of Aorta in Five Areas of World (males, aged 20 to 59, ppm ash, median values)*

ELEMENT	UNITED STATES	AFRICA	NEAR EAST	FAR EAST	SWITZERLAND
Essential					
Chromium	1.9	5.5	11*	15*	30*
Manganese	8	13*	18*	22*	9
Iron	2900	2800	4600	5600*	2300
Copper†	91	110	180*	160*	110
Non-Essential					
Aluminum	28	840*	1000*	450*	69
Barium	7	14*	19*	19*	17*
Nickel	<5	7	24	21*	13*
Silver	0.1	<0.1	1.4*	1.0*	<0.1
Titanium	<5	20*	59*	20*	12
Bulk					
Calcium %‡	5.0	3.3	2.9	2.4*	6.6
Phosphorus %	7	6	13*	10*	8

*Differs from United States value, $P < 0.001$
†Decreases with age, $P < 0.001$, $r = -0.51$
‡Increases with age, $P < 0.001$, $r = +0.43$
Data from Tipton et al.[49]

human equivalent of 0.5 to 0.7 mg. per day to be in adequate balance; man receives 0.05 to 0.1 mg. in his food and water.

As chromium is necessary for glucose and lipid metabolism,[40] it is likely that the decreased or absent aortic chromium in atherosclerosis reflects the decreased or absent chromium in the coronary arteries, and that this leads to abnormal metabolism and plaque formation. The intermediary steps, however, have not been determined. Until the natural organic complex of chromium is obtained for therapeutic trials, it will not be possible to reverse this condition in man, if the condition is reversible.

Other Metals

We can examine a number of other elements for differences in aortic concentrations from the United States, Africa, Near East, and Far East (Table 6), bearing in mind that atherosclerosis is widespread in the United States but is less severe in the other areas, and that differences in elemental content could reflect primary or secondary effects. Calcium and phosphorus levels declined as the presumed severity of atherosclerosis of the aorta decreased, from the United States to Africa to the Near East and to the Far East. Of 20 elements, 11 showed aortic concentrations significantly different from those in United States aortas; three of these were the essential trace metals chromium, manganese, and copper, which were higher in Near and Far Eastern samples than in those of United States subjects. Of the non-essential metals, five—aluminum, barium, nickel, silver, and titanium—had significantly higher concentrations in foreign than in United States aortas. From what is known of the innate toxicities of these metals, it is doubtful that aluminum, barium,

Table 7. *Trace Elements Considered Involved Experimentally in Cardiovascular Diseases*

	PROTECTIVE	INDUCTIVE
Atherosclerosis	Cr, Mn, V, Co	Co (injected), Cu, Cr Deficiency
Hypertension	Zn	Cd, Zn Deficiency
Aortic calcification	F, Mg	F deficiency
Elasticity of arteries	Li, Cu	
Focal myocardial necrosis	Se	As

Adapted from Masironi[18]

silver, or titanium has other than a secondary nonspecific role in atherosclerosis. Therefore, from this indirect viewpoint, we must examine the possibility that deficiency of chromium, manganese, copper, or perhaps nickel could be a causal factor in the disease—chromium, copper, and manganese are listed as protective in Table 7. The elements which did not vary significantly in aorta from area to area are the essential: magnesium, vanadium, potassium, cobalt, zinc, molybdenum and non-essential cadmium, lead, strontium, and tin.

The function of chromium has been discussed. Manganese inhibits experimental atherosclerosis in rabbits and influences lipid metabolism in atherosclerotic patients. The manganese content of the heart and aorta of atherosclerotic subjects is lower, and that of plasma is higher, than in healthy controls.[18]

Copper induces atherosclerosis in experimental animals.[11] Human subjects with a history of myocardial infarction had elevated serum copper concentrations.[10] Soft waters corrode copper pipes. Aortic copper in atherosclerosis is depressed, whereas myocardial copper is increased. Copper deficiency causes defective synthesis of aortic collagen and elastin, interfering with elasticity of blood vessels. In American aortas, ash and calcium increased with age, and presumably atherosclerosis (correlation coefficients, r, 0.43 to 0.51, $P < 0.001$) whereas copper and potassium decreased with age ($r = -0.51$ and -0.70 respectively, $P < 0.001$). Thus, copper may play a regulatory role.

Table 8. *Secondary Changes in Trace Elements in Atherosclerosis and Myocardial Infarction*

	INCREASE	DECREASE
Atherosclerosis		
Aorta	Fe, Mo, Co, Pb, Ag, Zn	Cu, Li, Mn, Cr
Heart	Co, Cu, Zn	Mn
Plasma, or blood	Mn	Zn
Myocardial Infarction		
Injured tissue, heart	Ba, Br, Sb	Mn, Mo, Al, Rb, Co, Cs, Zn
Serum	Cu, Ni, Mn, B, Mo, Ca	Zn, Fe
Urine	Cu	

Adapted from Masironi[18]

Secondary changes of trace elements in atherosclerosis and myocardial infarction are shown in Table 8. Six metals are increased in aorta, 4 are decreased; the 4 may be etiologically involved. Six elements increase in serum; 3 are diagnostic of infarction. The injured myocardium collects 3 strange elements and loses 7, 4 of which are essential. Most of these changes reflect abnormal tissue.

HYPERTENSION

Excessive vasospasm leading to a permanent elevation of the blood pressure is a common phenomenon in civilized man. Whereas there are many factors in the genesis of hypertension—emotional, psychosomatic, nervous, endocrine, and renal—there is one common denominator in most cases, and that is altered arterial reactivity.

Successful treatment of hypertension is accomplished by two types of chemical agents, one of which acts on nerves and the other on blood vessels. The latter group are all chelating agents, complexing metals: hydralazine, EDTA, BAL, thiocyanate, nitroprusside, azide, and the like.[29] Thus, it appears that a metal is somehow involved in hypertension.

Experiments were conducted on rats fed for life small doses of each of 20 metals in drinking water, in a metal-free environment.[46] Blood pressures, heart weights, and microscopic sections were evaluated. The only trace metal causing hypertension was cadmium.[26] Cadmium accumulated in liver and kidney in concentrations common to civilized man,[42] and in blood vessels. When it was removed by injecting a zinc-loaded chelating agent, Na_2Zn CDTA, blood pressure became normal within a few minutes, and remained so.[39, 43] Zinc replaced some cadmium in liver and kidney. This agent is undergoing clinical trials.

Cadmium hypertension in rats duplicates moderate human hypertension in having elevated blood pressure, increased mortality, renal arteriolar sclerosis,[19] enlarged hearts, and increase in the severity of atherosclerosis.[37] Deaths from hemorrhage are common. The blood pressure of rats is extremely sensitive to dietary cadmium (Table 9) and when cadmium is virtually absent in the kidneys it is low. As our diet is deficient in cadmium (0.07 micrograms per gram) and as commercial diets contain sizable amounts (0.25 to 0.60 micrograms per gram) it is clear that all experiments which have been done on animal hypertension are complicated by renal cadmium, unless efforts at a cadmium-free environment were made. An intake of 1.0 ppm cadmium in rats is accompanied by demonstrable effects on fertility, viability of young, carbohydrate metabolism, and SGOT activity.[47]

Human deaths from hypertension were associated with more renal cadmium, or a higher ratio of cadmium to zinc, than were deaths from coronary heart disease or accidents. Likewise deaths from cerebral vascular disease were accompanied by more cadmium and a higher ratio than accidental deaths (Table 10). There was a good correlation of clinical death rates from hypertension by country and renal cadmium.[25] Human hypertensive patients excreted 40 to 50 times as much cadmium in their urines as did normotensive controls, a phenomenon unrelated to proteinuria.[23]

Table 9. *Effects of Cadmium in Food and Water on Systolic Blood Pressure of Rats*

AGE, MONTHS	0.1 PPM CD B.P. mm. Hg	0.62 PPM CD B.P. mm. Hg	5.1 PPM CD B.P. mm. Hg	P*
Females				
3	85 ± 2.2	109 ± 3.2	–	<0.001
4	87 ± 4.4	110 ± 3.7	–	<0.001
5	81 ± 2.2	112 ± 6.1	–	<0.001
7	–	115 ± 4.0	–	<0.001
12	84 ± 5.8	–	211 ± 8.3	<0.001
13	82 ± 3.4	–	–	–
17	92 ± 4.9	–	182 ± 12.6	<0.001
24	84 ± 3.8	–	205 ± 10.9	<0.001
30	99 ± 4.2	–	229 ± 12.9	<0.001
Males				
12	106 ± 5.7	–	124 ± 5.6	<0.025
17	94 ± 3.8	–	122 ± 4.5	<0.001
24	79 ± 3.6	–	137 ± 6.2	<0.001
30	93 ± 5.1	–	198 ± 7.9	<0.001
Females, 17				
Calcium in water			92†	
No calcium			253‡	<0.001
Renal cadmium, ppm	0.03 ± 0.002	2.0 ± 0.21	54.7 ± 4.82	<0.0001
Hepatic cadmium, ppm	0.03 ± 0.008	1.2 ± 0.18	20.9 ± 3.91	<0.0001

*P is significance of difference between the 2 groups shown.

†8 rats normotensive, 2 hypertensive (260 mm. Hg)

‡All of 10 rats hypertensive

In all groups but three given calcium, there were 16 to 24 rats. In the third column, 5.0 ppm cadmium was given in water. Data from Kanisawa and Schroeder[15]

Table 10. *Renal Cadmium (ppm ash) and Cadmium Zinc Ratios in Human Kidneys According to Major Cause of Death*

CAUSE OF DEATH	NO. CASES	CD MEAN μg/g	P*	CD/ZN MEAN μg/g	P*
United States Mainland					
Hypertension	17	4220	–	0.77	–
Accidents	117	2940	<0.0005	0.62	<0.01
Arteriosclerotic heart disease	27	2660	<0.0005	0.62	<0.01
Miscellaneous	26	3380	N.S.	0.58	<0.01
Foreign					
Hypertension	17	5080	–	0.94	–
Accidents	23	3170	<0.025	0.66	<0.005
Arteriosclerotic heart disease	12	2430	<0.01	0.49	<0.005
All cases					
Cerebral vascular accident	23	4266	–	0.80	–
Traumatic accident	140	2980	<0.0005	0.62	<0.005

*P is significance of differences of mean from hypertension or cerebral vascular accident.

Data from Schroeder[25]

These data indicate that cadmium is a causal factor in rat hypertension and probably in human hypertension. Against the latter hypothesis is the work of Morgan[20] who failed to confirm our observations on a group of negro subjects in Alabama. Negroes in the United States are peculiarly sensitive to hypertension, differing from whites in this respect.

There is a further paradox in this theory. Overdoses of cadmium do not cause hypertension, but induce renal damage and emphysema. Also, continuous ingestion of enough to cause osteomalacia—Milkman's syndrome—does not lead to hypertension. The overt toxicity of cadmium negates hypertension—recondite toxicity produces it. This situation also holds for industrial workers exposed to cadmium in air.

Air levels of cadmium were significantly and highly correlated with deaths from hypertensive heart disease in 28 urban areas of the United States.[4] Cadmium occurs in cigarette smoke,[36] a known factor for coronary occlusion. The industrial consumption of cadmium has increased since 1940 at an exponential rate.[2] Cadmium alters vascular reactivity.

DISCUSSION

As one views the large amount of work on trace elements and cardiovascular diseases, it becomes clear that at least two metals are involved directly, and two others may act conjointly. In the first place, atherosclerosis is consistent with a deficiency disease of some function of carbohydrate and lipid metabolism. Two trace metals—chromium and manganese—are concerned with carbohydrate and lipid metabolism. Deficiency of chromium resulting from the use of refined foods is probably prevalent in this country. Deficiency of manganese in human diets consisting largely of refined foods is also possible. Although human requirements are not known, pigs need 40 ppm and cattle about the same amount, whereas human beings receive 2 to 5 mg. per day in a 2 kg. diet. Losses of 86 per cent from wheat by milling, 89 per cent from raw sugar by refining, and 75 per cent from rice by polishing could easily contribute to relative manganese deficiency. Manganese was low in Type A school lunches in this country.[22]

Manganese is involved in glucose utilization, and deficient animals showed reduced tolerance to ingested glucose, like chromium-deficient animals.[18] It is also involved in lipid metabolism, stimulating the hepatic synthesis of cholesterol and fatty acids. Manganous ion is a cofactor for mevalonic kinase, which synthesizes squalene and cholesterol. Whereas we do not know which of these two similarly acting metals is deficient (both could be), the weight of evidence favors chromium, for there is no manganese deficiency, either dietary or tissue, in rats exhibiting chromium deficiency and atherosclerosis.

The other trace metal believed causal in cardiovascular disease is cadmium as a factor in hypertension. Cadmium and zinc are intimately related, and are bound by the same protein—a high-cysteine, low-tyrosine molecule which is synthesized only in response to cadmium. They are metabolically antagonistic. Zinc is essential for many enzymatic reactions in all living things. Zinc has been found to have an increasing

Table 11. *Experimental Counterparts of Human Cardiovascular Diseases. Trace Metal Imbalances.*

ABNORMALITY	RATS	HUMAN BEINGS
Atherosclerosis, Cr. deficiency		
Glucose tolerance	reduced	reduced
Response to Cr	normal	normal in 40–50%
Serum cholesterol	elevated	elevated
Response to Cr	reduced	moderately reduced in 40–50%
Aortic plaques	induced	? induced
Response to Cr	prevented	?
Status of tissue Cr	deficient	deficient, especially aorta
Hypertension, Cd excess		
Blood pressure	elevated	elevated
Response to Zn chelate	lowered	moderately lowered
Renal arteriolar sclerosis	present	present
Cardiac enlargement	present	present
Renal cadmium	40–60 ppm	40–80 ppm
Renal Cd:Zn ratio	>0.58	>0.70
Atherosclerosis	increased	increased

number of therapeutic actions on a variety of human disorders—anosmia, growth, sexual development, delayed wound healing, burns, ulcers of legs, postalcoholic cirrhosis of the liver, tolerance to ingested alcohol, and atherosclerotic ischemia of the legs, or peripheral vascular disease.[8, 9, 12, 14, 24, 30] Experimentally zinc has been found to be involved in DNA and RNA synthesis, learning behavior, protein metabolism, carbohydrate metabolism, reproduction, bone growth, integrity of skin, as well as in many enzymes. Analytical deficiency of plasma zinc is widespread,[9] found in pregnancy, women taking antifertility steroids, many older people, cases of burns, atherosclerotic complications, leg ulcers, atherosclerosis, and several chronic diseases, such as tuberculosis, infections, leukemia, some cancers, malnutrition, and uremia. Marginal zinc intakes come from the same sources as do marginal chromium and manganese intakes—refined grains, sugars, and fats.

The most striking clinical effects of oral zinc are on peripheral vascular disease.[12] Doses of 150 mg. a day as the sulfate have caused improvement in the circulations of ischemic extremities, heart, and probably brains. Improved circulation is associated with no rise in blood pressure distal to an obstruction of an artery of a leg. This phenomenon indicates vasodilitation specifically in ischemic areas. The net results have been improvement in ischemic pain and dysfunction, healing of early gangrene, return of pulses to normal, and improvement of angina pectoris and cerebral ischemia. We have observed favorable effects with 30 mg. a day as the acetate, about double the usual adequate dietary intake.

The mechanism of action is not known, but it may involve the displacement of cadmium from ischemic arterial wall by zinc in excess.

That chromium and cadmium may not be the whole story in respect to trace elements and cardiac disease is suggested by microscopic find-

Table 12. *Interstitial Focal Myocardial Fibrosis in Rats Fed Various Trace Elements for Life in Drinking Water*

ELEMENT	DOSE ppm	NO. RATS	FIBROSIS No.	FIBROSIS Per Cent	P	MYOCARDITIS, FOCAL
Controls	–	44	1	2.3	–	–
Selenate	3	64	1	1.6	N.S.	–
Tellurite	2	35	2	5.7	N.S.	–
Nickel	5	30	4	13.3	N.S.	–
Niobium	5	58	11	18.9	<0.25	1
Zirconium	5	54	12	22.2	<0.025	1
Lead*†	25	29	7	24.1	<0.025	–
Vanadium	5	27	7	25.9	<0.01	–
Antimony†	5	42	12	28.6	<0.01	–

P is difference from controls by Chi-square analysis

*Males only

†Recondite toxicity in terms of longevity

Note: These sections of heart were all read by J. B. Blennerhasset, M.D., of the Department of Pathology, Massachusetts General Hospital, Boston.

ings on sections of hearts from rats fed 8 trace elements for life. Focal myocardial fibrosis – scars visible grossly which resemble healed myocardial infarcts microscopically – were found in a variable proportion of rats (Table 12). There were significantly more in rats given niobium, zirconium, lead, vanadium, and antimony than in those fed nickel, tellurium, selenium and in the controls. Myocarditis, or recent infarcts, were seen in 2 animals. Possible significance of these chance findings lies in the ability of niobium to displace vanadium, zirconium to displace chromium, and in the recondite toxicity of lead and antimony, which shorten life span and longevity of rats.

CONCLUSIONS

Imbalances of trace metals may influence cardiovascular diseases causally, or may be involved secondarily. Chromium deficiency is a causal factor in atherosclerosis; manganese may also be deficient in this disease. The experimental evidence supports this theory, in that a replica of the human disease was developed in rats and prevented by chromium fed or in foods (Table 11).

Cadmium is a causal factor in hypertension. A replica of the human disease was developed in rats and cured by removing the causal factor by chelation. Zinc deficiency could also play a part in hypertension (Table 11).

Zinc given orally is a useful therapeutic agent in peripheral vascular disease even with gangrene, and also has favorable effects on ischemic hearts and brains.

The definitive roles of trace elements in the two major cardiovascular diseases deserves further study.

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The Etiology of Atherosclerosis

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The data of the foregoing papers provide the basis of a reasonable account of the etiology of atherosclerosis. The basic factor, the *sine qua non*, is the multiplication of the intimal cells in response to pressure changes caused by hydrodynamic forces (see page 257). Demonstrating the striking correlation between the development of the lesions and the locale of the forces has been a major contribution.

A second major contribution has been the concept advanced by Zilversmit and Newman;[11] it points out the role of the endothelium in excluding lipids from the intima. This phenomenon has been shown to consist actually of an equal movement of lipid in and out.[6] When the intima becomes abnormal, the movement into the arterial wall preponderates. There is also an endogenous production of lipid within the intima and this is affected by enzymic factors (see page 293).

Superimposed on the intimal abnormalities produced by hydrodynamic factors are additional lesions produced by carbon monoxide that enters the blood as a result either of smoking or of exposure to gasoline engine exhausts. Thus most of the so-called risk factors, i.e., hypertension, obesity, and smoking (see page 323), are readily understandable. The role of physical activity, although seemingly important in clinical studies, has yet to be explained.

The role of diet remains unproved, despite the efforts of various agencies to consider it established. Actually, these agencies have all declared that the effect of diet has never been proved. The statistical methods used to establish the importance of serum cholesterol level as a risk factor have been shown to be of dubious validity.[4, 7] As regards atherosclerosis in animals, the findings are the reverse of those expected on the basis of the dietary theory; i.e., animals who take frequent feedings of a diet that contains a large amount of unsaturated fat have more atherosclerosis than those who gorge themselves with fat meat at widely-spaced intervals (see page 281).

Attempts to produce atherosclerosis in animals by cholesterol feeding have yielded ambiguous results.[1-3] The interpretation offered by some workers that these experiments indicate that diet-induced hypercholesterolemia causes atherosclerosis has been demolished by the observation

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that intimal changes occur within a few days after cholesterol feeding has begun, weeks before the serum cholesterol rises (see page 245). The responsible mechanisms are unknown, although it was shown many years ago that on standing cholesterol is readily oxidized to other compounds.[9] It is probable that it is one of these compounds that damages the intima and ultimately leads to cholesterol deposition in it. If this can be established, an important reason for the very high incidences of atherosclerosis in developed as compared to undeveloped countries suggests itself. Millions of pounds of dried egg-yolks are used annually in commercial baking in the industrialized countries. If the cholesterol in this powdered dried egg-yolk suffered the same oxidation, the product would rapidly damage the arterial intima, as in Lee's experiments, without elevating the serum cholesterol level, as in Lee's experiments (see page 281). The pastry of the coffee-hour or the luncheon may be as potent a factor in atherogenesis as the smoking habit, obesity, and hypertension.

Sugar has a proven part in the production of certain hyperlipemias in some persons. As such it may play a secondary role in atherogenesis (see page 351).

Atherosclerosis is a reversible disease.[8] Genetic factors seem to be important.[5] Abnormal platelet function perhaps plays a role, probably a secondary one.[10]

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Physiology in Acute Myocardial Infarction

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The exact mechanism responsible for the injury of myocardial fibers leading to infarction is not known. Although occlusion of an artery is the usual precursor, infarction may occur without occlusion when the coronary circulation is compromised by disease and a marked decrease in diastolic pressure occurs. In some cases a great increase in cardiac work may have the same effect. The myocardial damage is clearly due to an imbalance between the energy requirement of a beating heart and the energy supply afforded by an impaired circulation. Although this basic process is readily apparent, its mechanism of damage is not. Since the oxygen tension within cells is normally only 1 or 2 mm. Hg, a tension of zero is quickly reached if the muscle cells are contracting. On the other hand the accumulation of metabolites is an equally likely cause of damage. (This does not include acidosis, since the human heart can tolerate a pH of 6.8 and the canine heart of 5.6 for at least half an hour.) At any rate, there is nothing to indicate that giving oxygen in an attempt to save the damaged myocardium does any good unless enough pulmonary congestion is present to interfere with oxygenation of the blood in the lungs. The role of widespread coronary vasoconstriction induced by reflexes from local acute damage, from the chilled skin, and from the distended abdominal viscera is similarly ambiguous.

The effects of myocardial infarction are variable in occurrence and intensity. Some are of only diagnostic or prognostic significance and others require active treatment if the patient's life is to be saved.

Pain

The precise mechanisms underlying the production of pain by myocardial ischemia are unknown.[1] Years ago Lewis showed that exercising a muscle under conditions of ischemia causes pain, an observation confirmed by others; however, there is no precise information indicating whether the lack of oxygen or the excessive production of some metabolite is the direct cause of the discomfort.

The nerve fibers that carry coronary arterial pain run in the adventi-

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tia of these arteries. They are carried in the middle and inferior cardiac nerves and the thoracic cardiac rami to the middle and inferior cervical and the first four thoracic posterior roots. These axones are small, poorly myelinated or unmyelinated, and their rate of conduction is slow; they therefore resemble sympathetic motor neurones except that they run to the cord as a simple fiber without any synapse in the ganglion between a preganglionic and a postganglionic fiber. Other components of the pain of coronary disease, such as pain in the neck or jaw, are apparently carried in the vagus nerve. The fact that most of the pain-carrying fibers enter the cord in the first four or five thoracic segments accounts for the typical referred pain over the skin of the shoulder, arm, or inner fingers. Anginal pain may be referred to a phantom limb. The skin temperature over the painful arm is low, owing to reflex vasoconstriction.

Fever

The occurrence of fever, or the changes induced by fever, (i.e., leukocytosis, accelerated blood sedimentation rate) is one of the features that distinguishes myocardial infarction from other syndromes of cardiac pain. The fever clearly is due to tissue necrosis, but why it begins 12 to 36 hours after the onset of pain, in contrast to the immediate fever of pulmonary infarction, is not known. Fever persisting for more than a week, or elevation of the sedimentation rate prolonged for more than 6 weeks indicates continuing necrosis and hence a poor prognosis.

Circulatory Dynamics

Lowering of the output of the heart usually occurs following myocardial infarction.[1] The reported finding of decreased blood flow through the fingers is difficult to interpret with certainty since the circulation in the hands is strongly influenced by neurogenic factors and may not indicate the state of the circulation as a whole. The arm to tongue circulation time is normal or slowed. The right atrial pressure (currently misnamed "central venous pressure") is also variable. Left ventricle end-diastolic pressure may be elevated in patients with cardiac pain but there is no conclusive way to decide whether this is due to (a) myocardial failure or (b) a change in cardiac tone, or (c) both. The peripheral venous pressure may be normal, low or elevated. Elevations may be due to cardiac decompensation or to a rise in intrapleural pressure consequent to bronchospasm.

Of special interest is the finding by different authors of low values for venous pressure in some instances, suggestive of a state of shock caused by impaired peripheral vascular mechanisms. In this connection the observation of temporary loss of tone in the small vessels is particularly pertinent.

Hemoconcentration, evidenced by an increase in hematocrit level, often follows acute myocardial infarction. The plasma and blood volumes are low in many patients, at least initially. This is probably caused by the associated acute pulmonary edema that occurs in most cases. However in patients in whom chronic cardiac decompensation develops, the plasma volume may increase.

In general, except for the low cardiac output it is impossible to char-

acterize the circulatory phenomena consequent to myocardial infarction *per se*, for it is probable that the cardiovascular changes that have been found are determined largely by the occurrence of associated conditions such as hypovolemic shock, pulmonary edema, congestive heart failure, and cardiac arrhythmias.

Shock

The shock that occurs in association with myocardial infarction is of several types and has various implications. It may be immediate in onset or may develop after a few hours. In some cases severe hypotension (together with pallor and cold sweating) develops with or within minutes after the onset of pain. In many cases this condition is self-limited and of short duration. It appears to be neurogenic in origin. It may occur spontaneously or it may be precipitated by moving the patient, particularly after he has been given an injection of morphine. In other cases the shock is caused by the primary fall in cardiac output caused by the death of a portion of the heart muscle. This too may be of limited duration; given time, the heart may make adjustments that compensate, at least temporarily, to astounding amounts of myocardial destruction.

The neurogenic shock of myocardial infarction requires no treatment except perhaps for some vasoconstrictor drug. (It is important to maintain the diastolic blood pressure, since coronary artery blood flow largely depends on it.) Although digitalis increases the force of contraction of even a partially infarcted heart, its use in shock is contraindicated because of the splanchnic vasoconstriction the drug induces. This vasoconstriction not only may lead to mesenteric infarction—admittedly not very common— but it also induces the release from the ischemic gut of substances that depress myocardial function and hence perpetuate and aggravate cardiogenic shock.

A second main type of shock that accompanies myocardial infarction is that produced by pulmonary edema. When edema of the lungs develops, blood plasma becomes trapped in the lung's interstitial tissues or is lost into (or through) the alveoli. This loss may amount to half a liter, and the resulting hypovolemia may induce or aggravate shock. The possible role of generalized hypoxia secondary to the pulmonary edema in inducing shock cannot be evaluated in individual cases. In any event, the hypovolemia may be aggravated by powerful diuretics, by venesection, or by tourniquets.

Pulmonary Edema

This disorder is probably neurogenic in origin for it occurs irrespective of whether the left or the right ventricle is the seat of infarction, and is usually relieved by morphine alone. Much work must be done in this field; the vast amount of theorizing that occupies space in the medical literature has little established validity.

The fact that the arterial blood oxygen saturation is lowered in many patients with myocardial infarction suggests that pulmonary edema is more commonly present than recognized. It must be remembered that interstitial pulmonary edema may cause no rales or wheezes but it does impair oxygenation of blood.

Whether the hemoconcentration caused by pulmonary edema is a factor in the development of the phlebitis and pulmonary embolization that occurs after myocardial infarction can only be conjectured.

Cardiac Arrhythmias

The occurrence of ventricular arrhythmias, that is, extrasystoles or tachycardia, after myocardial infarction is probably consequent to the formation of hyperirritable foci in the damaged ventricular myocardium. The possible role of digitalis in this phenomenon should not be ignored. It is probable, however, that the other common arrhythmias in this disorder are vagal in origin. For example, it has been shown that atropine may abolish partial heart block after myocardial infarction; available evidence also suggests that atrial fibrillation and flutter are due to vagal reflexes acting on the atria. This explains the frequent occurrence of atrial arrhythmias in patients in whom all or most of the damage is in the ventricles. A very rapid arrhythmia may aggravate or produce hypotension.

Autonomic Function

Reference has already been made to the probable vagal origin of some cardiac arrhythmias after myocardial infarction; it is likely that pulmonary edema seen in this condition is also reflex. The gastric distention and vomiting may also be vagal in origin. Definite evidence of increased vagal tone is afforded by the development of hypersensitivity of the carotid sinus reflex after myocardial infarction.[1]

The occurrence of bluish pallor, cold skin, and also a reduction in peripheral blood flow all suggest sympathetic stimulation. Additional evidence in this regard is the not uncommon finding of a level of arterial blood pressure above what is usual in a given patient early in the course of myocardial infarction. Excretion of metabolites of adrenal medullary hormones may increase.

Intermediary Metabolism

Data are available that suggest the occurrence of an "adaptation reaction" after myocardial infarction.[1] Eosinopenia is common. Lymphopenia also occurs. Adrenal cortical hormones or their derivatives may be excreted in excess. Creatinuria develops early; a negative nitrogen balance soon becomes manifest, as well. Similarly, a disturbance of carbohydrate metabolism appears, with elevation of the blood lactate and pyruvate levels. Glycosuria and hyperglycemia are well known to occur, either de novo or as evidence of the making of overt or latent diabetes mellitus. The appearance of severe glycosuria in a patient previously known to be free of this finding is indicative of a severe adaptation reaction and hence is a better indication of a poor prognosis than are the electrocardiographic changes. The finding of elevated blood cholesterol levels with normal cholesterol ester percentages immediately after myocardial infarction probably are consequent to the "adaptation reaction" in some cases.

Blood Clotting

A tendency toward intravascular clot formation is common after myocardial infarction. Blood clotting measurements have been found to

be accelerated by some authors. The responsible mechanisms are unknown but may include the effects of bodily injury per se, increased viscosity of the blood owing to dehydration or the loss of plasma into or through edematous lungs, the action of catecholamines and slowing of the blood flow consequent to shock, congestive failure, or oversedation.

In addition, clots may form on an area of damaged endocardium.

An interesting phenomena that has received little recognition is embolization months after the apparent healing of a myocardial infarct. In such cases a ventricular mural thrombus, incompletely organized by ingrowing granulation tissue, may undergo internal proteolysis; the osmotic effect of the peptides and amino acids that accumulate may give rise to swelling and finally rupture of the mural thrombus.

Pericarditis

Pericardial friction rubs are common after myocardial infarction but tamponade does not occur except as a result of cardiac rupture or of bleeding caused by excessive doses of anticoagulants.

Healing

The necrosis of myocardial cells stimulates the proliferation of surviving capillaries and fibroblasts in situ and the ingrowth of others from the circumjacent areas. Healing is well advanced by the fifteenth day and the scar is probably completely formed in 6 or 8 weeks. Necrosis and replacement by scar of an extensive mass of myocardial tissue may leave nonfunctional areas in the ventricle; these sometimes take the form of large aneurysms and as such interfere with the expulsion of blood from the ventricle during contraction.

Liquefaction of the necrotic myocardium may procede more rapidly than organization of the infarct by granulation tissue. In such cases rupture of the ventricle may occur, usually between the fifth and fifteenth days after the infarction. This is almost always fatal. It is unpredictable, and septal perforation may occur. This complication causes physical signs and also changes in the circulation resembling those of congenital septal defects.

Renal Function

The generalized vasoconstriction that follows myocardial infarction involves the kidneys to a variable degree. In some cases it is enough to cause albuminuria: With the development of shock the renal blood flow is greatly diminished and hence the excretion of urea is greatly retarded. A rise in blood urea nitrogen level is common, and is especially rapid and marked when protein breakdown is increased by the adrenocortical hormones released during the alarm reaction. This results in a large amount of nitrogenous material being poured into the blood stream, where it remains if renal function is not adequate to remove it. Accordingly the amount of rise in blood urea nitrogen level is of some prognostic significance.

Chronic Cardiac Decompensation

The physiology of chronic cardiac decompensation, involving in its manifestations the whole body does not differ from that of chronic heart

failure from other causes.[1, 2] It occasionally disappears spontaneously, apparently because of the healing of the cardiac lesions.

The failure may have several different causes. One—probably the least frequent—is widespread patchy fibrosis of the myocardium. More commonly the fibrosis involves mainly one area, and if this is large enough, the presence of noncontractile tissue in the ventricle wall may prevent the efficient development of pressures in the ventricle during systole. This may occur even though most of the ventricle is still normal. In extreme cases the nonfunctional ventricle wall may bulge out when the rest of the wall contracts, giving the picture of a ventricular aneurysm. In other cases the ventricular attachments of the chordae tendineae may become fibrosed and the function of the mitral valve thereby distorted.[3] The combination of cardiac dilatation together with functional derangement of valve action often leads to mitral insufficiency.

THE STIFF MYOCARDIUM SYNDROMES

There is now a considerable literature on the functional myocardial disorder caused by myocardial infarction and by chronic coronary artery disease. This disorder manifests itself by increased stiffness—so called "decreased compliance"—a condition that seriously disrupts myocardial function.[1-8, 10-12] Compliance determines left ventricular diastolic pressure and the relations between right and left ventricle filling pressures. Accordingly it has marked effects on cardiac function.

One effect of decreased left ventricle compliance is impaired pump function. When this impairment is severe, shock—so-called "cardiogenic" shock—develops.[10] Although this shock syndrome is due to pump failure, there is no evidence whatsoever that digitalis ameliorates it.[5, 9, 10]

Another consequence of the decreased left-ventricle compliance of coronary artery disease is a rise in end-diastolic pressure. This rise was formerly always taken to be synonymous with ventricle failure but in the circumstances discussed here the finding has no such significance.[6] The rise in end-diastolic pressure caused by decreased compliance, when transmitted back through the mitral valve, leads to an increase in pulmonary venous and capillary pressures. Accordingly the development of pulmonary congestion, and perhaps edema, is to be expected. The usefulness of digitalis in this type of pulmonary congestion and edema is doubtful.

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Physiologic and Clinical Actions of Nitroglycerin

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Inorganic nitrite and organic nitrate compounds, particularly glyceryl trinitrate (nitroglycerin), are the most widely used antianginal preparations. The clinical effectiveness of this class of drugs in relieving anginal pain was first described by Brunton[7] in 1867 and Murrell[31] in 1879. Since then, numerous investigators have attempted to explain the physiologic basis for the therapeutic effects of these agents. Two main hypotheses have been proposed. The first is that the drugs act directly on the coronary circulation; the second attributes relief of anginal pain to their effects on cardiac dynamics.

Sites of Action

Nitrites cause relaxation of most smooth muscles of the body, including vascular, ureteral, uterine, gastrointestinal, and bronchial. Their cellular action has been attributed to uncoupling of oxidative phosphorylation[35] and to inhibition of the breakdown of arterial adenosine triphosphate (ATP), a potent vasodilator.[38]

Types of Preparations and Routes of Administration

Nitroglycerin given sublingually is the drug of choice for treatment of the acute anginal attack, or for administration prophylactically prior to an activity known to cause angina in a given patient. (Because it is effectively absorbed sublingually, this route of administration will be the point of reference throughout the present report unless otherwise specified. Whether or not controlled-release oral doses of nitroglycerin will prove clinically useful is still under investigation.[37]

The most commonly used long-acting nitrate preparations are erythrityl tetranitrate, isosorbide dinitrate and pentaerythritol tetranitrate. Both oral and sublingual forms are available. While some patients

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may benefit from these preparations, especially in the sublingual form, little advantage over sublingual nitroglycerin in improving exercise capacity can be demonstrated under controlled laboratory conditions.[25] At present, only nitroglycerin ointment appears to offer true long-acting (> 3 hours) improvement in exercise performance.[55] In this regard it should be noted that the evaluation of antianginal agents by subjective means alone can often be misleading since a large proportion of patients with angina respond as well to placebos as to pharmacologically active agents.[5]

EFFECTS ON THE CORONARY CIRCULATION

The animal studies of Essex et al.[21] and Boyer and Green,[5] performed more than three decades ago, indicated that intravenously administered nitroglycerin caused an increase in coronary blood flow. More elaborate flowmeter techniques have found this effect to be exceedingly transient, however. Coronary blood flow usually increased only during the first 20 seconds after infusion of the drug and was followed by a period of normal coronary flow, and then a period of reduced flow as the systemic blood pressure fell and cardiac work was reduced.[47, 66] Sublingual nitroglycerin (even at high doses) had little effect in increasing any phase of coronary blood flow in dogs.[26, 47]

In contrast to the flowmeter studies, radioisotope experiments in dogs[4] have shown a decline in myocardial blood flow following both intravenous and sublingual administration of nitroglycerin, but an increase with direct intracoronary administration. It should be noted that only because of the design of the latter study could the peripheral (extracoronary) circulatory effects of the drug be avoided. As alluded to earlier, systemic hypotension induced by nitroglycerin may lead to autoregulatory alterations in coronary blood flow and mask any primary effects of the drug.

Whether or not an increase in overall coronary blood flow occurs is therefore moot. Studies of regional myocardial blood flow, however, suggest that nitroglycerin may effect changes in local circulatory conditions. It has been reported to cause redistribution of blood flow toward the subendocardium both normally[71] and after coronary occlusion.[3, 46, 71] However, other studies, using different experimental techniques,[23] have demonstrated a reduction in both subendocardial blood flow and myocardial contractility after either intracoronary or intravenous administration of nitroglycerin, suggesting the possibility of a "coronary steal" effect under certain conditions. In other canine studies with chronic coronary artery obstruction produced experimentally, Fam and McGregor[22] have shown that both intravenous and sublingually administered nitroglycerin caused an increase in collateral flow to the occluded coronary artery. More recently Cohen et al.[14] demonstrated that this effect occurs only during regional (rather than global) ischemia. When the whole heart is ischemic, the collaterals are fully dilated and unresponsive to nitroglycerin. These findings are of particular importance when studies in man are considered (see below).

Methods such as those used in the acute animal experiments de-

scribed above are not applicable to intact man, and more indirect methods for determining myocardial blood flow have been used. These studies depend on clearance principles and measure blood flow per unit mass of muscle. Unit myocardial blood flow in patients with coronary heart disease is similar to that of normal controls, and is not related to the degree of coronary artery disease.[32, 60] Administration of nitroglycerin alters this similarity. Brachfeld et al.[6] reported an increase in coronary blood flow and myocardial oxygen consumption in normal subjects and those with mild cardiac disease after sublingual nitroglycerin, while in subjects with angina pectoris Gorlin et al.[30] found no change in either myocardial blood flow or oxygen consumption. In both of these studies, the nitrous oxide method of determining myocardial blood flow was used.

Other investigators have reported both confirmatory and opposing findings. Cowan et al.,[7] utilizing a bolus injection of rubidium-84, reported a significant increase in coronary blood flow in arteriosclerotic subjects after sublingual nitroglycerin was administered. Bernstein et al.[4] using xenon-133, did not find an increase in flow in their subjects. When the drug was administered by the direct intracoronary route coronary blood flow did rise, although to a lesser degree in patients with advanced coronary artery disease. To further confuse the issue, several groups, including Likoff's,[43] have observed dilatation of the large coronary arteries after administration of sublingual nitroglycerin. These angiographic observations may be misleading, however, in that increased caliber of a large artery bears no necessary relationship to tissue blood flow.

One possible explanation for these varied results is that myocardial blood flow is non-uniformly distributed when coronary artery disease is present. It is likely that what is being measured by clearance methods reflects primarily muscle perfused by normal coronary arteries. Abnormally slow flow rates through diseased vessel segments are represented by slower clearance rates which may be masked by the faster components deriving from normally perfused areas. Thus, myocardial blood flow in man is at best an "average" of flow dominated by high flow or normal components.

Additional evidence to support the concept of varying regional myocardial blood flow has been obtained by Liedtke et al.[42] using dye-dilution curves to measure myocardial transit time. When the dye is injected into coronary arteries (and subsequently sampled from the coronary sinus) transit times are longer through diseased vessels as compared to normal ones. Cannon et al.,[8, 9] using xenon-133 photoscanning, and Sullivan et al.,[65] using krypton-85 washout techniques during cardiac surgery, have both demonstrated patchy zones of poor perfusion in areas supplied by diseased vessels. Most importantly, clearance curves measured in anatomically identified zones of poor perfusion were faster after nitroglycerin administration, presumably representing increased blood flow through collateral vessels to areas distal to coronary artery obstruction.[33]

That nitroglycerin may improve regional myocardial blood flow without affecting total flow is an intriguing explanation for some of the diverse results reported with this drug. Nitroglycerin may augment collateral flow by dilatation of the large artery segment distal to the stenotic area, with the subsequent increase in the pressure gradient across the

stenosis favoring both antegrade and collateral inflow. It may also selectively dilate collateral vessels themselves, as suggested by canine experiments.[14, 22]

EFFECTS ON CARDIAC DYNAMICS

In both dogs[26] and man,[6, 30] the administration of nitrites results in varying degrees of systemic hypotension. The hypotensive effect is short-lived following intravenous administration (5 minutes) and longer following sublingual administration (15 to 30 minutes). Pressures in the pulmonary circulation also fall.[6, 30] In addition to arterial vasodilatation, venous vasodilatation occurs, resulting in the pooling of blood in the peripheral veins.[45] Consequently, there is a reduction in right and then left ventricular filling pressures (pre-load) as well as in impedance to ventricular ejection (after-load). Ventricular dimensions are reduced, especially in end-diastole,[70] and stroke volume and cardiac output usually fall, despite a reflex increase in heart rate. How these circulatory changes affect the anginal state will be discussed in the next section, but it is of interest that despite these reductions in the hemodynamic indices which usually affect myocardial oxygen consumption, reduction in this parameter has not been consistently described in either animal or human subjects. In man, for example, some investigators reported increases,[6] others no change,[30, 60] and still others have reported a decrease[4] in myocardial oxygen requirements after nitrite administration.

MECHANISM OF ACTION IN ANGINA PECTORIS

In considering how the physiologic actions of nitroglycerin help to explain its beneficial action in alleviating anginal pain, it is necessary also to consider the pathophysiology of the anginal state itself. Although angina can be present in a variety of disease states (hypertension, aortic valvular disease, anemia, thyrotoxicosis, etc.) for purposes of this review we shall limit our discussion of angina pectoris to its most commonly associated pathologic condition—coronary artery disease.

Two mechanisms have been proposed as the underlying basis for the anginal state: absolute reduction in coronary blood flow and/or increase in mechanical activity of the heart beyond flow capacity of all or single segments of the coronary circulation. As discussed earlier, blood flow per unit of myocardium in patients with coronary artery disease has been reported to be similar to that of normal subjects when measured in the resting state.[32, 60] Furthermore, when patients with coronary artery disease are subjected to varying kinds of cardiovascular stress—exercise,[13, 48, 53] isoproterenol infusion,[13, 36] or atrial pacing[15, 24]—coronary blood flow increased in all reported studies but one.[36] The increase in flow paralleled the increase in mechanical activity of the heart.

Most investigators support the hypothesis that angina is usually due to increased cardiac mechanical effort in the face of limited coronary blood flow reserve. Observations during attacks of spontaneous or effort-

related angina have shown an increase in heart rate, and systemic arterial and ventricular end-diastolic pressures.* The latter has been attributed to either transient left heart failure or reduced ventricular compliance. Central to all these studies is the observation that myocardial oxygen consumption is determined for the most part by three mechanical variables: heart rate, contractile state, and developed systolic stress, the latter a function of intraventricular pressure, volume, and wall thickness.[63] When myocardial oxygen requirements exceed ability to increase myocardial oxygen consumption, myocardial ischemia ensues and may be accompanied by anginal pain.

Nitrites are effective in relieving myocardial ischemia and angina pectoris in part because they decrease the mechanical activity of the heart through reduction in left ventricular pressure and volume.[19, 41, 50] This is secondary to relaxation of the smooth muscles of the arterial and venous systems.[4, 45] The drug has no apparent direct effect on the contractile state of the heart but increases heart rate as a reflex response to lowered blood pressure. Posture is important when the effects of nitroglycerin (or any of the nitrites) are evaluated. In the supine position venous return is greater and exercise tolerance lower.[40] A common example is the development of angina in certain patients following exercise only after they have assumed the recumbent position. Accordingly, the hemodynamic and anginal-relieving effects of this class of drugs are most marked when the patient is sitting or standing.[12] By reducing the mechanical effort of the heart nitroglycerin also increases exercise capacity in patients with coronary disease.[11, 54, 57] A greater total body workload can be performed before the cardiac workload at which angina occurs is reached. Similarly, studies of atrial pacing tachycardia indicate that after nitroglycerin is given, hemodynamic abnormalities are not as readily manifested, and the heart can be paced at faster rates without development of chest pain.[10, 25] Whether or not nitroglycerin can improve abnormalities of ventricular wall motion remains to be demonstrated.

In addition to the effects of the drug on cardiac dynamics, there is also evidence that it can affect coronary blood flow during angina. An absolute reduction in coronary blood flow has been reported in an occasional patient during spontaneous angina pectoris. In one such patient coronary blood flow was measured after nitroglycerin was administered; coronary blood flow was restored to pre-anginal levels and anginal pain relieved.[29] Nitrites may also improve distribution of flow in angina induced by effort. Because of obstructive coronary atherosclerosis, *segments* of myocardium are inadequately perfused during increased cardiac mechanical activity even though *average* coronary blood flow is often increased. Nitrites have been shown to increase flow to areas of poor perfusion at rest,[31] and may well do the same during periods of increased cardiac mechanical activity.

Nitroglycerin may also be used in combination with other drugs, including beta-adrenergic blocking agents and digitalis. Propranolol, the most widely used of the beta-adrenergic blocking agents, has been shown by Wolfson and Gorlin[72] to reduce myocardial oxygen requirements by a

*See references 1, 13, 27, 31, 44, 48, 52, 53, 58, 59, 62, 67, 69.

marked reduction in heart rate and myocardial contractile state, with relief of anginal symptoms. The reflex tachycardia that accompanies nitrite-induced vasodilatation and hypotension is blocked by propranolol and thus the two drugs may act in a complementary fashion to reduce myocardial oxygen requirements and increase exercise tolerance.[18, 56, 61, 68] Digitalization may also be of benefit to patients with angina pectoris, but only in those subjects demonstrating cardiomegaly or left heart failure.[64] By decreasing the size of the heart (and wall tension) digitalis can reduce myocardial oxygen requirements and lessen the need for nitroglycerin.

In summary, it is not clear whether one or both of the principal types of action of nitroglycerin, i.e. to redistribute myocardial blood flow or to reduce the mechanical work of the heart, is exclusively responsible for its beneficial action in angina pectoris. There are flaws in accepting either mechanism as a total hypothesis. The entire study of the effects of the drugs is complicated by the problem of separating primary effects from secondary ones.

THE CLINICAL USE OF NITROGLYCERIN

Nitroglycerin is an unstable compound but loss of potency can be minimized (less than 5 per cent after 200 days) when the tablets are stored in either clear or tinted glass vials.[19] If the preparation is still potent, a sublingual burning sensation is present[16] and most patients with typical anginal complaints will respond within 3 minutes to 1 or 2 sublingual tablets. Pain may be promptly relieved, or even prevented, when the drug is used prophylactically. The smallest effective dose should be used. This is usually 0.3 or 0.4 mg. The drug appears in the blood within 2 minutes after the tablet has dissolved under the tongue.

Occasionally severe hypotension occurs as a side effect. This can be especially dangerous in patients whose chest pain is due to myocardial infarction rather than angina. Although possible beneficial effects of nitroglycerin have been reported in acute infarction,[20] patients should still be cautioned to take no more than 2 tablets for any anginal episode and to call a physician if the pain is unrelieved by nitroglycerin and persists for 30 minutes or more despite cessation of activity. The most common side effects of the drug are headache and flushing. This at times may necessitate use of a smaller dose (0.15 mg.). Individuals who have continuous industrial exposure to nitroglycerin or other organic nitrates usually undergo symptomatic adaptation (i.e., vasoconstriction) to the vasodilatory effects of these drugs and side effects, such as headache, are usually minimal. Rarely, withdrawal from chronic nitroglycerin exposure has been associated with symptoms of ischemic heart disease, presumably from the now unopposed vasoconstriction. These symptoms are relieved by nitroglycerin and, except in a few instances, usually subside spontaneously within several days.[39]

Recently, in a group of patients with chest pain syndromes, Horwitz et al.[34] correlated the clinical and side effects of the drug with angiographic evidence of coronary artery disease. Patients with a chest pain

syndrome and a normal coronary arteriogram were less frequently relieved of pain and more often experienced severe or bizarre side effects than patients with coronary atherosclerosis. Thus, the drug appears to have diagnostic, as well as therapeutic, value.

CONCLUSIONS

Of all the nitrite and nitrate preparations, sublingual nitroglycerin appears to be the most efficacious in the treatment of angina pectoris. However, the mechanism by which the drug relieves anginal pain is uncertain. There is little evidence supporting the role of generalized coronary vasodilation, except in the normal circulation, but there is experimental evidence in both animals and man suggesting that the drug causes selective redistribution of blood flow to ischemic areas. By contrast, the relaxation of smooth muscles in the walls of arteries and veins induced by nitroglycerin has been demonstrated to cause a reduction in all parameters of cardiac mechanical activity except heart rate. Whether one or both of the effects, i.e., on coronary circulation or on cardiac dynamics, reflects the true mechanism of action of nitroglycerin is as yet undetermined.

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Coronary Heart Disease

Some Historical, Nosological, and Clinical Aspects

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This paper is dedicated with affection to the late Louis Wolff, M.D., that rarity among clinicians, whose intuitions and impressions have withstood the test of statistical study. With paternal patience he passed on to me much of what is recorded in the pages which follow.

The view that sudden obstruction of a coronary artery was incompatible with life for more than a few minutes persisted into the twentieth century, in spite of isolated reports of death delayed for hours, days, or even weeks after a presumed sudden occlusion of a coronary artery. The way was prepared for a change in this view by Herrick's exposition in 1912 of the clinical features which permitted the ante mortem diagnosis of sudden obstruction of a coronary artery, and his statement, "Death is the result in nearly all these cases. Yet it may be delayed for many days. More than this, there is, as has been shown by reference to experimental work, no intrinsic reason why some patients with obstructions of even large branches of the coronary artery may not recover."[6] The concept was slow to gain a place in everyday practice. The third edition of Sir James MacKenzie's *Diseases of the Heart*,[7] published in 1914, does not distinguish terminologically between the brief, repetitive attack of angina pectoris and the prolonged, severe, and sometimes fatal attack—both are called angina pectoris. And even a decade after Herrick's paper, clinical teaching at the Massachusetts General Hospital was that angina pectoris followed by fever carried an ominous prognosis.[15] Nevertheless, the idea that instances of cardiac pain could be divided into two main groups—angina pectoris and coronary obstruction (or myocardial infarction)—gradually gained acceptance. As the distinction came to be made, it became amply apparent that Herrick was right; an occlusion need not inevitably lead to prompt death.

At this time the electrocardiogram was being introduced into clinical medicine, despite the objections of Einthoven who originally turned down Wenckebach's request for a clinical electrocardiograph on the grounds that clinicians regularly spoiled all good tools for physiologic research.[5] As more and more tracings were recorded from patients with

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prolonged pain, it became apparent that the classification which recognized only angina pectoris and "coronary obstruction" was clearly inadequate. (There was, of course, the additional problem that the three and then the four lead electrocardiograms might miss the signs of infarction even when it was present.) The terms "preliminary pain in coronary thrombosis,"[4] "impending acute coronary occlusion,"[11] and "impending myocardial infarction,"[14] were introduced in recognition of the problem posed by the existence of pains which were neither stereotyped angina pectoris nor "acute coronary artery occlusion." The terms failed to solve the problem because not all the prolonged attacks eventuated in coronary occlusion/thrombosis or in infarction of the myocardium.

More useful was the concept for which the term "coronary failure" was coined by Blumgart and co-workers[1] in 1940, to designate an intermediate group of cases with pain persisting longer than is usual in repetitive angina pectoris but without evidence of tissue necrosis. This had the advantage of removing the label "impending" when nothing further might happen. This is the sense in which the term "acute coronary insufficiency" (or "coronary insufficiency") is now used most commonly, dating from a 1947 publication of Master et al.[8] The objections to this term are that (1) angina pectoris and acute myocardial infarction are just as surely instances of coronary insufficiency as is the intermediate syndrome, and (2) the term has meant different things to different people, having been used in the literature prior to 1947 by Master himself and other co-workers[9] with a quite different meaning, namely "recent myomalacia without coronary occlusion." They pointed out that the patchy necrosis was usually associated with some factor which increased the work of the heart or diminished coronary flow. This specific meaning is no longer remembered today; what has happened is that Blumgart's concept has been widely adopted using Master's term for it and the original description has, accordingly, been credited mistakenly to Master rather than to Blumgart.

Both of these terms are relics of the era of four lead electrocardiography and antedate the use of serum enzymes in cardiac diagnosis. Both have doubtless been applied many times to cases which today would be recognized as acute myocardial infarction. It seems apparent, therefore, that cases so diagnosed today are frequently not comparable to many cases so labeled 30 years ago. It is time that these terms be abandoned; the merit they had at one time in broadening our conceptual understanding of coronary heart disease has been lost in a world of improved diagnostic skills.

Other terms which should be abandoned include "arteriosclerotic/atherosclerotic heart disease"—the designation applied by the New York Heart Association to heart disease resulting from atherosclerotic disease of the coronary arteries.[10] Too often students and physicians misunderstand this as referring to disease of the heart secondary to generalized atherosclerosis. Undoubtedly, such disease does, in fact, exist, for the pressure work of the heart is increased in the patient with generalized atherosclerosis as manifested by loss of vessel elasticity and raised systolic blood pressure. This condition has as valid a claim to the term atherosclerotic heart disease as does heart disease secondary to disease of

the coronary arteries themselves. I do not suggest that we invite further confusion by so renaming it at this stage; it may just as readily go on being referred to as "systolic hypertension due to atherosclerosis with secondary involvement of the heart." This is a long, unwieldy term, but we must recognize that our attachment to short, catchy terms which do not quite express what we have in mind is one of the sources of our confusion. In place, then, of the current terminology "arteriosclerotic/atherosclerotic heart disease," the term "coronary artery heart disease," or more simply, "coronary heart disease" is more precise and less likely to be misunderstood. It has the further advantage of not precluding from inclusion in the *clinical* classification, those cases in which spasm of coronary arteries or disease of small vessels rather than atherosclerosis of the main coronary arteries seems to be the problem.

The preferred English term, "ischemic heart disease," has caught on in this country.[13] It also allows inclusion of functional obstructions and small vessel disease, but seems to me to invite confusion with electrocardiographic terminology which classically separates three grades of involvement, namely, ischemia, injury, and necrosis. "Ischemic heart disease" and "coronary heart disease" jointly suffer the shortcoming that they do not permit reasonable classification of the rare case of angina pectoris, myocardial infarction, and death in the presence of an apparently normal coronary arterial tree. Ischemic episodes are spoken of, though it is frequently not clear whether this refers to episodes—even infarctions—in the course of "ischemic heart disease," or episodes in which the electrocardiographic abnormalities are limited to T wave changes. I prefer, lest confusion result, to reserve the terms ischemia, injury, and necrosis for use in describing electrocardiographic patterns. In my role as a clinician, I have not the slightest hesitation, however, in making a clinical diagnosis of infarction when I feel it is warranted, even if the electrocardiogram shows only T wave changes (ischemia). Conversely, in my role as electrocardiographer, I refer to a *pattern* of ischemia or injury even if I know the total clinical picture is diagnostic of infarction. The electrocardiogram, in short, is only one of the data on which the diagnosis is based; and the integration of all the data into a clinical diagnosis is the job of the clinician, not the electrocardiographer.

The difficulty is compounded by two other problems: (1) tracings taken by chance during one of a hundred identical attacks of angina pectoris and submitted to the laboratory without the information that the tracing was recorded during pain may be read in language which suggests to the unwary clinician that the changes are of greater significance than he may have anticipated; and (2) the electrocardiographer finds himself searching for words to express his extra worry and concern when, for example, T wave changes, presumably a transient phenomenon, last longer than he thinks they should. Somehow, ischemia seems too mild a diagnosis, yet injury or necrosis as diagnoses are not warranted electrocardiographically. For this situation, and for the acute ST changes which are increasingly and incorrectly referred to as ischemia we often prefer the term, "an acute myocardial process," thus forcing the clinician to consciously decide how much and how reversible is the alteration to the myocardium.

Other terms to which we object are "coronary occlusion" and "coronary thrombosis." These are suitable terms for the pathologist, but not for the clinician. They are commonly used when there is prolonged pain and electrocardiographic and/or enzyme evidence of tissue necrosis. Why not, then, use language which defines clearly what is known, namely, that there is myocardial infarction. To use the terms occlusion or thrombosis is to accept the discredited notion that infarction always implies an occlusion and, conversely, that occlusion always means infarction. Schlesinger,[12] Blumgart et al.,[2] and many others since have clearly demonstrated the fallacy of these assumptions.

The terms "preliminary pain in coronary thrombosis," "impending coronary thrombosis," and "impending coronary occlusion" are objectionable for the same reasons; and they and the term "impending myocardial infarction" should be dropped, for more than half the patients who may be so classified do not progress to clinically diagnosable infarction in the immediately following weeks. These objections are, perhaps, largely semantic; and certainly one may use them, and nevertheless, have a very good understanding of the clinical facts of coronary heart disease. Nevertheless, they tend to obscure some of these clinical facts and to confuse students.

Another misleading term is "anginal syndrome," for the word *syndrome* suggests a constellation of symptoms. Yet one of the major characteristics of angina pectoris is the fact that the discomfort tends to be the solitary symptom. When chest pain occurs simultaneously with shortness of breath, palpitation, sweating, etc., the likelihood is great that neurocirculatory asthenia rather than angina pectoris is the correct diagnosis.

The final term I have picked to plead against is "silent myocardial infarction." The term is used with two distinct meanings. My argument against the one is semantic, and against the other, conceptual. The word "silent" is often used when "painless" is intended. There can be no doubt that a significant number of myocardial infarctions are painless, but they are *not* asymptomatic. Thus, presentations with syncope, collapse, dyspnea, or in the guise of a cerebral vascular accident with complete resolution afterward are not rare. Furthermore, there are people who complain of pressure or of an unusual sensation in the chest, usually but not universally unpleasant, who insist that it is *not* pain. These people, some with symptoms other than chest pain or arm discomfort and others with pain equivalents – whether in the chest or arm, etc. – may be classified as *painless* infarction but not as *asymptomatic* or *silent* infarction.

Evidence for a second group of patients said to have suffered truly silent infarctions is two-fold: (1) the finding of infarction scars at autopsy, when it is too late to take a careful history; and (2) the finding of electrocardiographic evidence of infarction in living patients. In some of these reported in the literature, the term "silent" has been applied when a routine electrocardiogram showed an infarct not previously present.

These patients fall into several groups. In some the fact that a history entirely consistent with infarction could readily be elicited did not serve to remove them from the category of silent myocardial infarction into which they had been placed solely because they did not seek medical at-

tention at the time of the infarct. There are patients whose electrocardiograms are consistent with myocardial infarction and from whom no history of myocardial infarction can be obtained. Some may have had symptoms so mild as to have been forgotten years later; we have seen patients with symptoms so mild, that, had the diagnosis not been made fortuitously (e.g., because of a preoperative electrocardiogram), they would have been completely forgotten years later.

Others have such virtuosity in the production of symptoms that it is impossible retrospectively to weed out those symptoms of significance in relation to a certain illness from a catalogue of similar and dissimilar complaints. Still others would willingly confess their symptoms to the probings of a skillful enough examiner. A few are so sick and uncomfortable with other disease that the symptoms of the infarction seem trivial and go unmentioned. Rarely, there is congenital indifference to pain, though even in such patients we have seen infarctions diagnosed because of a "sensation" and a search. Then there are the silent patients, the psychotics who are either unaware of symptoms or unable to articulate their complaints. Finally, there are the few whose complaints do not enter consciousness because their brains are drunk, drugged, damaged, or anesthetized.

I have no doubt that many will disagree with my insistence that an asymptomatic infarction is a very rare event. I would ask any such to inquire of a busy electrocardiography laboratory how often an unsuspected acute myocardial infarction (acute in the sense that the electrocardiographic changes *evolve* under observation) is seen in which a history cannot be obtained despite a concerted attempt. The answer will be strongly at variance with the impression gleaned from the literature that silent infarction is a relatively common occurrence.

PROPOSED CLASSIFICATION

The classification which I propose in place of much of the current terminology to which I have raised objection had its start over a decade ago when Dr. Louis Wolff and I were the participants in a two-way radio grand rounds under the auspices of the Post-Graduate Medical Institute (Boston, Massachusetts). Our subject was pain in the chest related to myocardial infarction: the premonitory pains, the pain associated with the infarction itself, and the pain which might occur during the few weeks of hospitalization for infarction, and afterwards. We set about to codify what we considered to be the various presentations of coronary heart disease. The aim was a simple classification, one which did not depend on unproved assumptions, and one which eliminated terminology which was vague either semantically or conceptually. What evolved was a classification which was clinical, and, therefore, functional. It eliminated terms which beguiled the physician into thinking he knew more than he actually did. This classification has been previously published.[16]

The experience of a decade of use of this classification has convinced me that it furnishes a useful guide to therapy, that it simplifies record keeping, and that it provides a framework within which diagnosis, thera-

py, and prognosis can be discussed with other physicians and with the patients themselves. The classification is as follows:

Any patient who has pain attributed to the heart* or who has had such pain and/or an acute myocardial infarction is classified as having "coronary artery/arterial heart disease," or, more simply, "coronary heart disease." Having entered the classification of "coronary heart disease," he is then placed into one of three subgroups:

(1) chronic stable coronary heart disease;
(2) acute unstable coronary heart disease;
(3) acute myocardial infarction.

Note that by definition his condition cannot be stable without being chronic, nor can it be unstable without being acute.

CHRONIC STABLE CORONARY HEART DISEASE

This is the subgroup containing patients whose clinical status has remained unchanged for at least 2 months. Some are completely pain-free. Others have angina pectoris (chronic stable angina pectoris) but if they do, it follows an established pattern, is stereotyped in form, and occurs under predictable circumstances as often as there are adequate stimuli. Thus, a given patient may have somewhat more frequent attacks in the cold of winter than during the spring; and when he is upset or has eaten, less exertion may be required to precipitate an attack. Yet, in a broad general sense, the occurrence of an episode of angina pectoris is predictable, and it is this predictability which is the hallmark of chronic stable angina pectoris. Some patients fulfill this definition of stability from the very first attack of chest pain, but I do not classify them as *chronic* stable coronary heart disease until they have been stable for 2 months, for experience has taught that even the ones who seem stable from the outset are at increased risk for the first 2 months.

As a group, the patients in the category of chronic stable coronary heart disease have the best prognosis of all patients with coronary heart disease; and the outlook for those with angina pectoris is not necessarily worse than for those who are symptom-free. Some continue unchanged for years and even decades. Other patients undergo such slow and subtle change that no day-to-day variation is apparent, even though over long periods of time there may be a modest increase in the number of nitroglycerin tablets consumed. Those with angina pectoris may have complete remission at any time. With or without angina pectoris (provided that it is chronic and stable) these patients are as good surgical risks as age-matched controls who have not had clinical episodes of coronary heart disease.[3]

Conversely, patients may change abruptly from the category of chronic stable coronary heart disease by dying suddenly, developing an acute myocardial infarction, or entering a phase of acute unstable coronary heart disease. The latter presents the physician with an important

*Unless it is considered to be due to aortic stenosis or pulmonary hypertension.

diagnostic and therapeutic challenge. The instructions which I give to patients with chronic stable coronary heart disease are designed to provide treatment as long as stability persists and to guarantee my being alerted the moment there is a change. The patients need only follow these three rules: (1) prevent, (2) treat, and (3) report. The rules are spelled out to the patients as follows:

1. To the best of your ability avoid all activities and situations which you know from experience cause you discomfort in the chest. If something bound to cause pain is unavoidable, take nitroglycerin prophylactically, but do not use this as an excuse to abuse yourself.

2. If pain occurs unexpectedly, stop what you are doing, and take nitroglycerin for each such attack. Do not resume activity until all vestiges of the pain are gone. (The use of long-acting dilators and beta-adrenergic blocking agents does not alter the applicability of these rules.)

3. Notify me at once of any change in your symptoms, such as more frequent pain, spontaneous pain, new nocturnal pain, greater severity or different distribution of pain, or diminished response to nitroglycerin.

Any such change may signal the onset of acute unstable coronary heart disease.

ACUTE UNSTABLE CORONARY HEART DISEASE

The hallmark of acute unstable coronary heart disease is the new or unexpected. Thus, the unstable state may be signalled by (1) angina pectoris occurring for the first time, (2) recurrence of angina pectoris after remission for 2 or more months, (3) prolonged pain, or (4) any change in chronic stable angina pectoris. Let us look at these in some detail.

New angina pectoris may occur in a typical or atypical form. By typical, I mean that it is stereotyped; that is, it has the characteristics of chronic stable angina pectoris *except* that it is new. From the very beginning it is predictable; one episode is like the last and the next. Despite its apparent stability it represents a period of high risk to the patient and must be treated with caution. Atypical angina pectoris as used here refers to those cardiac pains – by no means rare early in the symptomatic history of coronary heart disease – which bear no clear relationship to exertion. Pain may occur unpredictably at rest or during modest exertion and remain in abeyance during far more vigorous activity. Sometimes the patient is wakened by pain. Paroxysmal nocturnal dyspnea in a patient free of prior heart disease and with a normal-sized heart has the same significance. Furthermore, the pain may vary in quality, duration, and location from attack to attack during this period. I am sure that the story of the patient who drops dead on the sidewalk outside the office of his physician who has just given him a clean bill of health is not apocryphal. Undoubtedly, many such patients go to their physicians precisely because they have chest pain, and doubtless in some of these instances the physician fails to grasp the significance of what he is told. This is probably the explanation of sudden unexpected death in young athletes, e.g., the football player who catches a pass and then drops dead.

Physicians insist that pain be stereotyped before they are willing to attribute it to the heart; they refuse to recognize that an electrocardiogram which remains normal during spontaneous pain or a negative exercise test (which is hazardous at this stage) *does not rule out acute unstable coronary heart disease;* and they fail, as a result, to institute a program of restricted activity which can be life-saving.

There is a group of cases variously labeled "coronary failure," "coronary insufficiency," "the intermediate syndrome," "impending myocardial infarction," "impending coronary occlusion," and "premonitory phase of infarction." We have stated above our objections to these terms. Nevertheless, they continue in use and, in general, refer to an episode of prolonged pain without evidence of tissue necrosis. Any such episode must be regarded as a manifestation of *acute unstable coronary heart disease*, the term we prefer to use.

Finally, any change in chronic stable angina pectoris must be regarded as a potential manifestation of acute unstable coronary heart disease. The change may be an increase in the frequency or the severity of attacks, a diminution of the stimulus required to precipitate an attack, etc. Other names used are prodromal angina, precursor angina, preinfarction angina, and crescendo angina. Any change in the characteristics of preexisting angina pectoris such as an increase in frequency or duration, pain of greater severity, different quality of pain, alteration in the distribution, a diminution in the amount of exertion necessary to precipitate an attack, the occurrence of spontaneous attacks, and less effect or none at all from nitroglycerin qualifies as a change from chronic stable coronary heart disease to acute unstable coronary heart disease. The terms angina decubitus for pain while recumbent and status anginosus for pain brought on by the very slightest of exertions add no additional information.

The preceding few paragraphs have contained a descriptive account of the clinical variations seen in symptomatic coronary heart disease. When any of these changes occurs, the greatest diagnostic efforts must be made, for not all apparent instability originates in the heart. The changes may be a reflection of extra demand made upon the heart by, for example, anemia, fever, thyrotoxicosis, or, as Heberden pointed out, "disturbance of the mind." In these patients the prognosis is no worse than that of chronic stable coronary heart disease once the contributing factor has been brought under control. When the change from chronic stable coronary heart disease to acute unstable coronary heart disease is the result of a change in the heart itself the outlook is far more serious. Some of the patients will, during their period of instability, have an acute myocardial infarction, some will die suddenly, some will return to a pattern of stability with an amount of angina pectoris which may be the same, more, or less than formerly, and some will have complete remission of symptoms. The term *unstable* is particularly suitable for it indicates that a change is to be expected. A change will generally be apparent within 2 months after the onset of the period of instability. Even when there is a change apparent earlier than two months, additional change may occur, and it is therefore advisable to wait for 2 months before regarding the period of instability as having passed.

Occasionally, status anginosus occurs as a manifestation of acute unstable coronary heart disease and persists longer than the two months usually required for stabilization. In many of these cases emotional influences seem to be at play. Status anginosus, however, is of limited value in determining the cause of instability; it may occur at the very onset of symptoms of coronary heart disease, it may rarely be a manifestation of an acute myocardial infarction, it may be triggered by extracardiac causes (especially tachycardia and emotional upsets), and it may occur as the agonal symptom in the natural history of coronary heart disease.

It has been my experience that a marked increase in the severity and/or the frequency of angina pectoris which is not related to an extracardiac cause, does not progress to acute myocardial infarction within two months, but persists at a markedly heightened level, and is almost always associated with a psychiatric problem; thus, so-called intractable angina pectoris as a "stable" state is exceedingly rare except as a manifestation of a psychiatric disorder.

Therapy for acute unstable coronary heart disease is both a challenge to and an opportunity for the physician. The change in a patient's program may vary from none whatsoever in the elderly sedentary person to treatment no different from that which might be imposed for acute myocardial infarction in the young and vigorous. It is my belief that the unstable state presents one of the best opportunities for the practice of preventive medicine in coronary heart disease, and that acute myocardial infarction can frequently be prevented if the nature of the symptoms is appreciated and sufficiently stringent restriction is imposed. Whatever the changes in the program may be, they must be made with knowledge of the existence, hazards, and duration of the unstable state.

It will be noted that we have included in a single category new angina pectoris, recurrent angina pectoris which has been in remission for 2 or more months, prolonged pain, and any change in chronic stable angina pectoris. The degree of risk of these diverse groups may be different and they may, therefore, be separated for the purpose of *investigation* of this risk. For *clinical* purposes, however, they belong together for each represents a risk greater than that present in chronic stable coronary heart disease.

ACUTE MYOCARDIAL INFARCTION

Acute myocardial infarction is a special case of acute unstable coronary heart disease. It is accorded a separate place in our classification because of the additional special risks and complications associated with it. External rupture of the heart, perforation of the interventricular septum, and papillary muscle dysfunction occur with acute myocardial infarction but not in the remaining cases of acute unstable coronary heart disease. Cardiac arrhythmias are known to be exceedingly common in acute myocardial infarction, but their exact incidence in acute unstable coronary heart disease without infarction remains unknown. They are nevertheless almost certainly the cause of sudden deaths which occur in this group of patients, though overall they are probably less frequent than

in acute myocardial infarction. Pulmonary edema is also less common in acute unstable coronary heart disease without infarction than in acute myocardial infarction. Nevertheless, the period of acute myocardial infarction and for at least two months afterward must be considered a period of instability.

It is, therefore, not surprising that recurrent pain following acute myocardial infarction is not uncommon. The pain may be indistinguishable from angina pectoris, or it may be prolonged, but in either case it may be a manifestation of the unstable state, provided that there is no evidence of extension of infarction or other cause of pain such as pulmonary embolism or fibrinous pericarditis. Recognition that one of the features of the unstable state is pain for no apparent reason solves the clinical dilemma and satisfies the demand for a definite diagnosis when the patient with an acute myocardial infarction has an episode of pain.

Patients with acute myocardial infarction may do well, progressing to the stage of chronic stable coronary heart disease with or without angina pectoris. On the other hand, death may occur at any time.

SUMMARY

It is my conviction that we do not need to await the results of new research to achieve a significant reduction in the mortality of coronary heart disease. If physicians will recognize that the unstable state exists and that it can be diagnosed from anamnestic data, if they will have the courage to prescribe marked activity reduction (at times to the extent of prolonged bedrest) when there are no objective data to go on, and if they will become sufficiently proficient in history taking to feel and transmit their own confidence about the diagnosis to their patients, much will have been accomplished. It may well turn out that there is more to be gained from placing acutely unstable but uninfarcted patients in the hospital with appropriate monitors, than from keeping in the hospital beyond 10 days those patients with acute myocardial infarction who have been completely free of complications up to that point. By my own definition the latter are still unstable, and I am not suggesting cavalier treatment of them. It is merely that facilities are not limitless and they must, therefore, be allocated to those patients at greatest risk and from among whose ranks may be expected the greatest salvage.

Clear-cut clinical classification of patients with coronary heart disease is a necessity. Many of the terms now in use are imprecise and confusing, and they should be dropped. In place of them I suggest that all patients with evidence of myocardial infarction and/or a past or present history of angina pectoris be classified as having *coronary heart disease.* They should then be further subdivided into one of the categories: (1) chronic stable coronary heart disease, (2) acute unstable coronary heart disease, (3) acute myocardial infarction. Experience with this classification has shown that it simplifies recordkeeping, discussion with other physicians, and explanations to patients themselves.

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Diagnosis of Angina Pectoris at the Present Time

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In the 200 years which have elapsed since Heberden's first report, his one sentence description has been repeatedly confirmed but seldom improved upon. "*Those, whose are afflicted with it, are seized, while they are walking, and more particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away, if it were to increase or to continue: the moment they stand still, all this uneasiness vanishes.*"

From the above it is evident that the term angina pectoris denotes a typical group of uncomfortable symptoms from which the patient seeks relief. Because there is nothing objective about this symptom complex, other terms, usually denoting some one component of the symptom complex or some related condition, have been used interchangeably. "Coronary insufficiency" is frequently used as a synonym, but is a physiologic term which really adds nothing to our recognition or understanding of the patients complaints and, in fact, may refer to different symptoms entirely, such as pulmonary edema.

Similarly, but more misleading, is the use of terms such as "coronary heart disease," "coronary artery disease," "arteriosclerotic heart disease," and so forth. Although it is true that the majority of cases of angina pectoris are accompanied by arteriosclerotic obstruction of the coronary arteries, this is not universally so; nor does such a pathological finding imply that symptoms necessarily occur.

In view of the recent interest in coronary arteriography it may be argued that to equate angina pectoris with coronary artery disease is a step forward and to try to separate the two is splitting hairs. After all, it may be reasoned that when the presence of coronary artery disease is discovered it should be corrected and thus the symptoms will be cured or prevented. In other words, coronary artery disease is the important diagnosis while angina pectoris is a more old-fashioned term. Without de-

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tracting from the value and promise of this most interesting new technique, there are reasons why the results of angiography cannot be accepted as a basic or final criterion for the diagnosis of coronary artery disease or angina pectoris.

Maximum information about the coronary circulation is gained with the injection-dissection method of Schlesinger.[5] In this postmortem technique, the right and left coronary arteries are injected simultaneously with different colored radiopaque lead-agar mass. The heart is then opened so that the major arteries lie in one plane and an x-ray film is made. With the film as a guide, the arteries are carefully dissected. This method shows the presence or absence of arterial occlusions or narrowing plus the presence of intercoronary anastamoses. The drawbacks are that it is time-consuming and can only be done postmortem. Angiography does not have these two drawbacks but it is much less accurate.

From the earlier Schlesinger technique it became evident that patients with angina pectoris all had heart disease and that most but not all had occlusions of one, two, or all three coronary arteries with inadequate collateral circulation. It was also evident that such abnormality was not specific for angina pectoris, for many hearts showed similar occlusions without the patients having experienced pain during life.[1, 6]

The proponents of angiography have acknowledged that angina may occur without coronary occlusions being demonstrable. However, the fact that occlusions may occur without angina has generally been ignored. The ability to demonstrate the existence of coronary artery disease during life is an important advance; however, we have yet to prove that the presence of coronary disease is necessarily accompanied by symptoms in the past, present or future. This is especially important in the absence of a sure cure.

Angiography is not a routine procedure. Considerable skill and special apparatus are necessary and these, as yet, are available in only few centers. This is not to denigrate the importance of this technique. It is essential, especially if we are to attempt surgical cure of coronary artery disease. However, the latter is still in the research or experimental stage and considerable time must elapse before its permanent value can be determined. This is especially true in view of the glowing reports of the results of previous surgical techniques which have nevertheless been abandoned.

The role of the blood pressure in the diagnosis and precipitation of angina pectoris has an interesting history. In the past, it was suggested that the finding of an elevation was helpful in diagnosis; more recently its role in increasing cardiac work has been considered to be an important factor in the precipitation of symptoms. Opportunities to obtain blood pressure readings just before or during attacks of angina pectoris are rare except when attacks are induced intentionally in the laboratory. Under such conditions the precipitation of angina by exercise was *followed* by blood pressure elevation but *preceded and accompanied* by either no change, or a rise or a fall. Hence, an elevation of blood pressure is not of universal importance in the diagnosis or the induction of angina pectoris.[1]

Similarly although the majority of attacks of angina pectoris are ac-

companied by electrocardiographic changes of S-T and/or T, characteristic of hypoxia, these do not invariably precede or accompany the pain, as can be shown by taking continuous tracings during angina induced by exercise.[5] Hence, electrocardiographic changes are of limited value in the diagnosis of angina pectoris.

A special word about electrocardiograms during spontaneous attacks is in order. Opportunities to obtain these are infrequent because of the short duration of attacks and lack of adequate warning. However, if one sees enough patients often enough one may be fortunate to have the electrodes in place when the pain occurs. Under such conditions the tracing will often show S-T depression and/or T wave inversion in the epicardial leads, i.e., evidence of hypoxia. These changes may be short in duration or may persist for minutes or even hours. At times they may be valuable objective evidence that the patient has a mechanism (i.e., transient hypoxia) which can produce pain. In the appropriate clinical circumstances (i.e., striking electrocardiographic changes during spontaneous pain but not before or after) they may be of great value in establishing or confirming the diagnosis. However, similar changes, although usually less in magnitude may be found in tracings taken periodically in patients with coronary artery disease without relation to concurrent symptoms.

In the absence of an objective test for the diagnosis of angina pectoris, the necessity for a clear reliable history becomes apparent. Patients, however, do not always report their complaints in a manner sufficiently clear or organized to permit diagnosis with assurance. Symptoms in the chest may originate in the gastrointestinal tract, the neuroskeletal system including the psyche, or the thorax including the heart. These symptoms may result from various types of disorders or may be functional in origin. Current publicity increases the apprehension of the public about chest symptoms and, hence, many symptoms which formerly might have been overlooked are now brought to the physician for diagnosis.

In obtaining the medical history, the physician must listen to the patient's story carefully, follow this by asking clarifying but not leading questions, and finally evaluate the result in the light of Heberden's criteria. Analysis of the histories of 100 patients who had been observed during attacks of angina induced by exertion showed that they each had five characteristics in common.[2] In contrast, patients in whom attacks of angina could not be induced were deficient in at least one of these characteristics. The five diagnostic criteria agreed with those of Heberden:

1. *Attacks are sudden in onset*, that is, there is little or no warning, and between attacks the patient feels perfectly well.

2. *The discomfort is in the anterior chest* in a region bounded by the anterior axillary lines, the suprasternal notch and the epigastrium. The upper or mid substernal region is the area most frequently involved. Radiation to the *inner* aspect of one or both arms is frequent but far from universal. Radiation to the jaw or mouth is rare, while radiation to the mid abdomen almost never occurs. Similarly, pain in the mid axillary line is not characteristic, nor is pain limited to the region of the cardiac apex. The area involved is not sharply delineated; the region is usually indicated by a sweep of a hand, not by a fingertip.

3. *The character of the discomfort is difficult to describe.* Although

uncomfortable, it is likely to be described as a pressing, squeezing, choking or smothering sensation rather than pain. Although often described as sharp, this usually means severe rather than knife-like. It is often accompanied or followed by belching but this is more likely to confuse than to help the diagnosis.

4. *Characteristically it is precipitated by exertion*, especially walking out of doors after meals or in the cold or the wind. This does not mean that attacks may not come on excitement or even while at complete rest, but the latter does not help in diagnosis.

5. *The attacks are short in duration*, for example, a few minutes but not characteristically a half hour or more. On the other hand, attacks that are momentary are not likely to be angina but may be premature beats.

These five diagnostic criteria are easy to remember with the employment of the mnemonic *SAVES* (*s*udden onset, *a*nterior chest, *v*ague character, *e*xertion precipitated, *s*hort duration). A sixth characteristic has become evident over the years and is often very helpful, namely the uniformity of attacks. Although there may be minor variations they practically always occur in the same area, have similar durations, and are of the same character. The differences are primarily in the ease of precipitation, the size of the area involved, and the severity of the discomfort.

The disappearance of the attack after the use of nitroglycerin is often used as an aid to diagnosis. This is not very reliable, however; many noncardiac symptoms apparently respond to nitroglycerin, while some patients are not certain of its benefits. More helpful diagnostically, in some patients, is the prophylactic benefit of sublingual nitroglycerin taken before exercise.

The fear of impending death mentioned by Heberden and emphasized so frequently in fiction is very rare, although it does occur. It is probably an individual psychological reaction.

In most instances heart x-rays and electrocardiograms are obtained but they are not very helpful in detecting chest pain. If positive, they offer objective proof of heart damage and hence supportive evidence of a potential cause of cardiac symptoms. Such studies are of greatest value in detecting basic damage, progress, or complications.

In recent years determinations of the cholesterol, uric acid and other blood constituents have often been made. These may be of value in treatment but, again, are of little help in precise diagnosis.

In most instances, a history adequate for diagnosis can be obtained at one visit but usually considerable time and patience is required because few patients are sufficiently observant or adequately vocal to describe their symptoms so that they can be translated into medical terms and evaluated readily. In some instances the precipitating cause, the character of the discomfort and its duration can only be obtained by frequent visits, with the patient being more observant as his attention is called to the details of the information desired. In a few instances consultation between patient and doctor may have to be repeated over months or even years before the details of the history become clear. In some instances the pictures at each visit may resemble angina in some respects but not in others. Under such conditions a lack of uniformity of the symptoms (especially in location) may be helpful in ruling out angina. The following

guideline has proved helpful. If after 2 years of adequate observation the history is not definitely that of angina pectoris it is advisable to consider the symptoms to be noncoronary in origin and to treat the patient accordingly.

Diagnosis is especially difficult if the history must be obtained through an interpreter. In many such instances the desire to be helpful results in the interpreter giving his impression of the doctor's questions and the patient's answers rather than exact translation. This, coupled with the side remarks between the patient and the "helper," may make it especially time-consuming and frustrating for the examiner.

The sparsity of objective proof of subjective pain may have medicolegal consequences. Even though no uniform relationship has been established between cardiac damage and the occurrence of pain, the judge, referee, or insurance adjustor at times, may refuse to accept disability or pain based on the patient's word alone without objective evidence of cardiac damage. Thus it may be difficult to collect damages for suffering or disability as a result of angina if there is no evidence of damage during or after an attack.

Similarly, the lack of objective proof of angina pectoris makes evaluation of therapy difficult and even raises problems in the selection of candidates for therapeutic studies. It is partly because of this lack of objective proof that modern diagnostic and therapeutic studies include coronary cineangiograms, exercise electrocardiograms, blood chemistry and blood gas determinations, and so forth. However, unless there is good reason to doubt the patient's integrity, the diagnosis must and can be made by painstaking and detailed history taking.

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The Treatment of Acute Myocardial Infarction

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Technical and pharmacological advances in the past decade have been accompanied by a decrease in hospital mortality from myocardial infarction. This has been accomplished primarily because of prompt and aggressive treatment of potentially life threatening arrhythmias. Nonetheless, myocardial infarction remains the leading cause of death in the United States. Since the majority of deaths occur before the victim reaches the hospital, it is clear that many patients who might benefit from available therapeutic techniques do not receive optimal care. The capability of initiating therapy during the earliest phases of myocardial infarction remains as one of the major medical challenges of the 1970's.

Prevention of coronary disease obviously is the ideal therapy but, at best, it will take many years for prophylactic public health measures to have any significant impact on cardiac mortality and morbidity. Identification of high risk individuals is necessary not only to initiate preventive treatment, but to educate such patients to seek medical attention promptly at the onset of premonitory chest symptoms.

Some medical centers have utilized mobile coronary care ambulances to bring specialized treatment directly to ill patients.[1, 67] Whether these efforts are likely to be effective or practical on a large scale basis is still unproven, but in any case the critical problem remains that of delivering patients to coronary care facilities with minimum delay in order to reduce the devastating high, early mortality. It is evident that the traditional practice of making a house call to evaluate a patient's chest pain is outmoded. The patient must be brought to a facility fully equipped for cardiopulmonary resuscitation. Even when patients arrive at hospital emergency rooms promptly, an efficient transportation process to the Coronary Care Unit (CCU) must be implemented, preferably utilizing portable monitoring and defibrillating equipment in transit. Since the early diagnosis of myocardial infarction is primarily based on clinical

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judgment and the electrocardiogram may be normal or nondiagnostic in the early hours of infarction,[84] an abnormal electrocardiogram should not be a prerequisite for admission to the coronary care unit. A liberal admission policy may increase the number of false preliminary diagnoses of myocardial infarction, but should result in more lives saved in the earliest stages of the disease.

Specific Pre-Hospital Care

Should the physician be present during the initial stages of infarction, he should institute medical therapy on the bases of the pulse rate and rhythm. Bradycardias are common, particularly with inferior wall infarction, and may predispose to more serious atrial and ventricular arrhythmias. With a regular rate less than 55 per min., atropine (0.5 to 1.0 mg.) is given intravenously. The risks of precipitating acute glaucoma, urinary retention, or paradoxical cardiac effects are insignificant relative to the margin of protection provided against ventricular arrhythmia. When the rate exceeds 55 per min. and there is evidence of cardiac irregularity, even though an electrocardiogram is not immediately available, a bolus of lidocaine (1.0 mg. per kg.) should be administered intravenously. Therapeutic blood levels can be maintained for as long as 45 minutes during transit to the hospital by giving 10 per cent lidocaine intramuscularly (4 to 6 mg. per kg.).[96]

Recently doubt has been expressed concerning the efficacy of atropine in acute myocardial infarction. Work, based primarily on animal studies that are not directly applicable to infarction in man, has indicated that slower heart rates are associated with a *lower* incidence of ventricular arrhythmias.[21, 22] Certainly overzealous rate acceleration is undesirable since tachycardia increases myocardial oxygen requirements and may further compromise already ischemic myocardium. Nonetheless, currently available clinical evidence supports the use of atropine for bradycardias, particularly those associated with pump failure or ectopic beats.

General Coronary Care Unit Care

Once the patient has been admitted to the coronary care unit, no therapeutic intervention should be regarded as "routine," but specific indications for drug use carefully weighed against possible side effects. On the other hand, efficiency is enhanced by a predetermined policy of patient care so that there is no ambiguity concerning orders, and nurses are encouraged to make clinical judgments and implement them if a physician is not immediately available. An example of a coronary care unit order sheet is shown in Figure 1.

The coronary care unit may be psychologically disrupting to the patient separated from his usual environment and surrounded with flashing lights and menacing equipment.[95] A vital responsibility of nurses and physicians alike is to discuss the coronary care unit routine with the patient, explaining what can be anticipated in the coming days. Although excess sympathoadrenal activity may induce arrhythmias after myocardial infarction, this aspect may have been over emphasized. It is well to recall the vivid account of a psychotic patient who terrorized a coronary

Standing Orders for Nurses in Coronary Care Unit*

1. Check vital signs immediately on admission to unit.
2. Start I.V. with 5% glucose and water, immediately. Use Intracath in arm vein, if feasible. If difficulty starting I.V., call resident to start cutdown.
3. Give any medications ordered by the physician on a *stat.* basis.
4. Attach the monitor to the patient.
5. Take a 12-lead ECG. Repeat daily for duration of stay in unit.
6. Give the patient a brief orientation to the unit.
7. Draw blood for CBC, prothrombin time, myocardial enzymes, clotting time and any other special tests ordered. Myocardial enzyme determinations repeated daily for 5 days.
8. Obtain urine specimens.
9. Check blood pressure every 15 minutes times 3, then every half hour times 4. If stable, then every hour unless otherwise ordered for the first 24 hours, then every 2 hours for the second 24 hours, then every 4 hours for the duration of stay in the unit.
10. Oral temperatures 4 times a day.
11. Apply anti-embolism stockings to both legs.
12. Record intake and output.
13. Portable chest x-ray daily for duration of stay in unit.
14. All these orders are subject to modification by the patient's physician.

*Courtesy of Pascack Valley Hospital, Westwood, New Jersey

Figure 1

care unit for 45 minutes, but caused no increased incidence of arrhythmias or mortality in any of the patients.[29] Sleep therapy has been suggested as a way of allaying anxiety, but the benefit of this is doubtful. Sleep itself may be stressful, electrocardiographic abnormalities having been recorded during rapid eye movement stages. Furthermore, large doses of sedatives may cause undesirable hypotension, shallow respirations, and depressed cough reflex, leading to various pulmonary complications. A quiet, well constructed coronary care unit run by a sympathetic staff is perhaps the safest and best form of tranquilization. Explanation and reassurance are sufficient to allay anxiety in many cases.

Certain other aspects of coronary care have changed in recent years. The traditional admonition against performing rectal examinations is of dubious validity.[18] Of greater importance, is the matter of optimal duration of strict bed rest and hospitalization. There is no conclusive evidence that drastic restriction of exercise is necessary or beneficial. In fact, dogs with experimental acute myocardial infarction permitted unrestricted activity had no greater incidence of rupture, aneurysm, or cardiac dilatation than dogs maintained at rest after infarction.[39] Deconditioning owing to prolonged bed rest may result in vasodepressor reactions when the patient is ambulated. In patients with congestive heart failure who have increased orthostatic tolerance the upright position is more physiologic. The major reasons for maintenance of bed rest during the first days after infarction are the presence of shock and a desire to reduce cardiac work. In one study the mean duration of bed rest after infarction prescribed by various physicians varied widely, from 7.4 to 15.2 days.[17] No clear reasons for this disparity were detected. It is likely that many patients are kept in bed and in the hospital for excessive and arbitrary periods of time that are not dictated by known facts about the course of the disease.

Many reports have advised reduction of the duration of bed rest and

hospitalization. In 1952, Levine and Lown stated that most patients could safely be placed in a chair by the third day.[48] In a recent study from Ireland of 295 patients surviving acute myocardial infarction, 18 per cent were discharged to their homes by the seventh day and 62 per cent spent 10 days or less in the hospital.[6] Providing that the clinical course was uncomplicated, late mortality was no worse in the liberally treated group. Another recent prospective controlled study indicated no apparent benefit to patients with uncomplicated myocardial infarction discharged after a 3 week hospital stay as compared to a 2 week stay.[36] Despite these data, of 2206 American physicians responding to a questionnaire in 1970 on patterns of care of acute myocardial infarction, the median hospital stay for all patients was 21 days with a median time before return to work of 2 to 4 months.[94] Although these figures may be overly conservative, they are in sharp contrast to the practice prior to and in the decade after World War II of 4 to 8 weeks of bed rest with return to work after 4 to 6 months.

It is clearly unwise to recommend a standardized method of treatment for all cases. Nonetheless, it is our opinion that in patients with uncomplicated infarction, commode privileges can be permitted even on the first day since the anxiety-provoking aspects of using a bedpan outweigh any potential benefits. Permission to sit in a chair may be granted during the first week. Chair time is gradually increased thereafter and followed by progressive ambulation, with hospital discharge generally between 2 and 3 weeks.

Coronary care unit treatment generally continues for 3 to 5 days, after which it is desirable to monitor the patient for another week on a medical ward or intermediate care unit. Since 30 per cent of hospital deaths occur after the sixth day,[30] half of these unexpectedly, a facility for post coronary care unit monitoring is highly desirable. When available, a portable tape electrocardiogram is useful shortly before discharge to document the presence of arrhythmias during ambulation undetected by routine electrocardiographic recording.

Oxygen Therapy

Although oxygen therapy is often initiated during transit to the hospital and in the early phases of coronary care, the evidence that it effectively enhances delivery to zones adjacent to the infarction is inconclusive. *In high concentration*, oxygen raises peripheral resistance, lowers cardiac output, and after prolonged administration may cause focal myocardial necrosis and pulmonary toxicity. Hypoxemia is a stimulus for coronary vasodilatation. Conversely, hyperoxemia produced by inhalation of high concentrations of oxygen causes vasoconstriction and reduced coronary flow.[86] In one study 100 per cent oxygen increased coronary sinus lactate in patients with arteriosclerotic heart disease indicating diminished total oxygen delivery.[4] Thus, overzealous administration of oxygen should be avoided since greater than normal arterial oxygen concentration does not necessarily augment myocardial oxygen availability, and may impair it.

Some degree of arterial hypoxemia is the rule after infarction.[41] The extent of unsaturation is proportional to the magnitude of functional derangement, marked hypoxemia occurring primarily in patients with

heart failure or shock.[71] Cardiac arrhythmias are usually observed with the more extreme degrees of hypoxemia. Arterial oxygen saturation less than 90 per cent rarely occurs after uncomplicated infarction, and in fewer than half of patients in shock or congestive failure.

The major indication for oxygen therapy is the presence of shock or congestive failure. Since deleterious hemodynamic and pulmonary effects are associated chiefly with high concentrations, oxygen is best delivered by nasal canula at a flow rate no greater than 6 liters per minute or with a Venturi mask to ensure inspired concentrations no greater than 40 per cent. The aim should be to restore the PaO_2 to normal (approximately 100 mm. Hg).

Analgesia

Morphine is the most widely used analgesic and also is of great value in the treatment of acute left ventricular failure.[92] When given intravenously its effect is almost immediate and peaks in about 20 minutes.

Although reduction of pain obviously is desirable, analgesia may be accompanied by hypotension, bradycardia, decreased cardiac output, and depressed respiratory drive, all potential precipitating factors in the genesis of arrhythmias. Meperidine has comparable hemodynamic effects, and possibly produces greater respiratory depression than morphine. Pentazocine does not cause hypotension, but in equianalgesic doses to morphine the degree of respiratory depression is similar, cardiac work may be increased and psychomimetic side effects are frequent.[38, 44]

Cumulative effects, interactions with sedatives and troublesome gastrointestinal symptoms are other clinical problems encountered with the use of narcotics. Often, non-narcotic analgesics are sufficient to reduce the intensity of pain. One approach is to assure the patient that some discomfort is to be expected and should be tolerated, and that in a few hours the pain will subside spontaneously. However, if pain is severe the nurse has been instructed to promptly give an analgesic. Using this method, we have been pleased at how infrequently narcotics need be administered.

Anticoagulants

After more than 20 years of controversy, there is still no unanimity regarding the role of anticoagulants after myocardial infarction. Despite numerous efforts, no study has satisfactorily met all requirements for valid statistical analysis.[25] Most observers agree that the major advantage of anticoagulants is for the short term prevention of venous thromboembolism. Therefore, patients most likely to benefit are those with such predisposing factors to embolism as shock, congestive failure, debility, or preexisting venous disease. Early ambulation, elevation of legs, isometric leg exercises, and elastic stockings all may have beneficial effects in addition to the pharmacologic effects of anticoagulants.[55]

In the absence of apparent contraindications, anticoagulation is generally initiated with heparin, either by infusion or by intermittent intravenous or subcutaneous injections. The Lee White clotting time before each dose should be maintained at 2 to 2½ times the control, but this test need not be performed frequently after the first few determinations. The activated partial thromboplastin time (APTT) is technically easier to

perform than the Lee White clotting time, and results are more reproducible. Using the APTT as a guide, heparin dosage should be regulated to maintain the APTT 1½ to 2 times the control value.[3] This is most conveniently done by a continuous intravenous infusion of heparin. Although there may be hypercoagulability during the first few days after infarction, there is no increased heparin requirement to sustain therapeutic clotting levels.[72] Heparin releases free fatty acids from chylomicrons and it had been suggested that this might potentiate arrhythmias.[42] Clinical confirmation for this, however, has been lacking.[76]

Since the effects of coumarin drugs are delayed, they may be initiated concomitantly with heparin, the latter being discontinued after 36 to 48 hours. Coumarin drugs interact metabolically with many other drugs used in the coronary care unit milieu particularly with sedatives. Therefore, fluctuations of prothrombin time can be anticipated when other drugs are being administered or their doses altered.

The advantages of long term therapy for uncomplicated myocardial infarction are small at best and are probably outweighed by the risk of hemorrhage. It is not surprising that the natural history of cornary disease has not been altered significantly by anticoagulants, since these drugs are generally ineffective in preventing arterial thrombus formation.

Perhaps the best approach to the prevention and treatment of arterial thrombosis is with drugs that affect platelet function.[32] Among the drugs currently under investigation are dipyridamole and aspirin, but substantial clinical trials have not yet been performed to ascertain their efficacy. Fibrinolytic agents (urokinase)[50] and arvin are also being studied as potential therapeutic agents.

Metabolic Factors

It is difficult to single out a critical metabolic factor in the genesis of arrhythmias associated with acute infarction, but it is likely that elevated catecholamines, local potassium loss, metabolic and respiratory acidosis, and high concentrations of free fatty acids alone or in combination play an important role.[66]

Sodi-Pollares proposed a metabolic therapy for myocardial infarction in which potentially toxic cardiac drugs are avoided and patients infused with an insulin, glucose, and potassium solution. Other investigators have been unable to confirm Sodi-Pollares' results, possibly because they used stereotyped infusions whereas Sodi-Pollares has stressed the importance of strict dietary control and a tailored intravenous solution based on the serum potassium concentration.[87] Differences in patient population also may have had a bearing on the disparate results.

ARRHYTHMIAS

Perhaps the most important single aspect of intensive coronary care is continuous monitoring of patients' heart rhythms and rapid treatment of observed abnormalities. For these objectives to be achieved, the nurses who staff the coronary care unit must be skilled in the diagnosis of car-

Standard Orders for Emergency Treatment of Premonitory Arrhythmias

1. In case of sudden onset of repetitive VPB, multifocal VPB, VPB interrupting the T wave, or more than 5 per minute in a patient in sinus rhythm the nurse administers a bolus dose of lidocaine (80 mg.) intravenously.
2. In case of sudden onset of any bradycardia (rate less than 50 per minute) or sudden onset of VPB (above criteria) in association with a preexisting bradycardia, the nurse administers a bolus dose of atropine (0.5 mg.) intravenously.
3. Further doses of these drugs must be specifically ordered by the physician.

Figure 2

diac arrhythmias. Even in a teaching hospital with a full complement of house staff, nurses should be able to defibrillate patients. When well trained physicians are not close at hand, nurses should be permitted to initiate therapy for certain premonitory arrhythmias, according to a predetermined set of orders (Figure 2).

It is helpful to classify arrhythmias as passive arrhythmias or bradycardias, and active arrhythmias or tachycardias. In the former the essential problem is depression of normal pacemaking or conduction, and therefore therapy consists of rate acceleration by drugs or electrical pacing. Tachyarrhythmias are due to acceleration of normal or ectopic pacemaker cells (enhanced automaticity) or reentry, or both, and therapy, when indicated, consists of suppressant drugs such as lidocaine. Distinguishing between these two groups may be difficult when more than one arrhythmia is present, but, in general, the slower the basic heart rate, the greater the likelihood that rate acceleration will be successful in restoring a regular rhythm and the greater the hazard of using suppressive drugs.

Arrhythmias may occur as the sole complication of myocardial infarction (primary arrhythmias) or as a secondary phenomenon in patients with congestive failure or shock. Although in one sense all arrhythmias are secondary to acute myocardial infarction, the distinction is a useful one, for with primary arrhythmias, therapy is directed at the arrhythmia (and in general results are good), while with secondary arrhythmias the underlying hemodynamic defect must also be treated. The success rate is lower in treatment of secondary arrhythmias, and often it is the hemodynamic derangement and the extent of infarction rather than the arrhythmia that determines the outcome in a given case.

BRADYCARDIAS

The sooner a patient is seen after the onset of symptoms of myocardial infarction the more likely he is to display a bradycardia. Adgey et al. observed that 47 per cent of patients with acute inferior infarction monitored within 1 hour were in sinus or nodal bradycardia or second or third degree atrioventricular block.[1] Many of these early bradycardias, including half of the patients with atrioventricular block, responded promptly to intravenous atropine.[67] Early bradycardias should be treated immediately, not only because they seriously compromise cardiac output and cor-

onary perfusion, but also because they apparently predispose to ventricular tachyarrhythmias at a time when the fibrillation threshold is greatly reduced. The initial treatment should be atropine, 0.5 mg., given as a bolus intravenously. The dose can be repeated every 3 minutes to a total of 2 mg. Should atropine fail to restore sinus rhythm, it is advisable to institute artificial pacing. Isoproterenol (2 mg. in 500 cc. 5 per cent dextrose in water) is sometimes effective as an emergency interim measure when atropine has failed, but may increase ventricular irritability and may increase the extent of myocardial necrosis by augmenting myocardial oxygen need in the early hours of infarction.[58]

Recently, Epstein and his co-workers have questioned the advisability of treating bradycardias unaccompanied by hypotension, suggesting that atropine may actually increase myocardial ischemia and augment, not diminish, the tendency to serious ventricular arrhythmias.[21] Although these suggestions were based on dog experiments, scattered clinical reports of apparent clinical deterioration after atropine was administered[59] also emphasize that atropine should be given cautiously, avoiding large doses and with care to avoid excessive rate increases, i.e., to rates over 80 per minute. A ventricular rate of 60 to 70 is satisfactory in most cases.

The same general principles apply to the treatment of bradycardias during the period of intensive care after the initial hours of infarction, although at this time vagotonia is relatively less important as an etiologic factor than edema, ischemia, or necrosis. Rates below 45 per minute should be accelerated regardless of the rhythm or the patient's clinical state. Patients with sinus rhythm and rates between 45 and 60 per minute may be left untreated in the absence of signs of ventricular irritability or hemodynamic embarrassment.

The later atrioventricular block occurs after the onset of infarction, the less likely it is to respond to atropine. In fact, the degree of block may be aggravated if atropine accelerates the atrial rate without improving atrioventricular conduction thereby increasing the number of blocked beats.[12] Like atropine, isoproterenol has an unpredictable effect on atrioventricular conduction, and frequent adjustment of the infusion rate is usually required to maintain a satisfactory ventricular response without inducing ectopic beats. Therefore, isoproterenol should be reserved for emergency use in patients with Stokes Adams attacks, asystole, shock, severe hypotension, or depression of consciousness prior to the institution of pacing.

There is considerable disagreement concerning the specific indications for pacing and prophylactic insertion of a pacing catheter in patients with intraventricular conduction defects and partial or complete atrioventricular block. Although prompt improvement occurs after initiation of pacing in some patients with complete heart block and some series of cases have suggested that early use of pacing is beneficial,[34, 69, 81] there has been no controlled study to evaluate the effect of prophylactic pacing. In the majority of cases it is the size of the associated infarction rather than the heart block per se which determines the patient's survival. Thus, complete heart block complicating anterior infarction is generally

caused by bilateral bundle branch block due to extensive septal infarction, and is associated with an unstable, slow, idioventricular pacemaker and an in hospital mortality of 85 per cent despite the prompt institution of pacing.[27] Power failure is the usual cause of death in such patients. On the other hand, when complete heart block complicates inferior wall infarction, the infarct is often not extensive, the atrioventricular block is usually caused by ischemia and edema (not infarction) of the atrioventricular node, is associated with a stable, even accelerated, atrioventricular junctional pacemaker, and is almost always transient. The prognosis of such patients even without pacing is relatively good. Nevertheless, since among patients with inferior as well as those with anterior infarction, there are individuals whose course is dramatically altered by pacing, we feel that prophylactic insertion of a standby pacer is often warranted.

Although it has been suggested that pacing is not an innocuous procedure in patients with acute myocardial infarction,[26, 69] this has not been our experience, nor that of others.[2, 73] In the course of 56 pacemaker insertions in 52 patients with acute myocardial infarction we encountered no instance of ventricular fibrillation or sustained ventricular tachycardia.[56] In experienced hands, the risk of pacemaker insertion in patients with acute myocardial infarction is quite small. Therefore, since the benefits of artificial pacing in patients with acute myocardial infarction are not only those that accrue immediately from correction of an existing bradycardia, but also the indirect benefit that digitalis and suppressant drugs can be employed safely in instances where they would otherwise be relatively or absolutely contraindicated, the indications for placement of pacing catheter should be rather liberal (Table 1). In most cases, pacing can be instituted at the bedside, thereby avoiding the need to transport the patient to an area where image intensifier fluoroscopy is available.

Table 1. *Indications for Pacemaker Insertion in Acute Myocardial Infarction*

1. Any bradycardia, rate less than 45, refractory to atropine.
2. Any bradycardia associated with low cardiac output or ventricular irritability refractory to atropine.
3. Complete atrioventricular block with narrow QRS complex, rate less than 50
4. Mobitz I (Wenckebach) second degree atrioventricular block, rate less than 50.
5. Complete atrioventricular block with wide QRS complex.
6. Mobitz II second degree atrioventricular block.
7. Acute right bundle branch block with QR in V_1.
8. Acute left bundle branch block.
9. Acute bilateral bundle branch block.
   a. Right bundle branch block with left anterior hemiblock.
   b. Right bundle branch block with left posterior hemiblock.
   c. Alternating left and right bundle branch block.
   d. First degree atrioventricular block with left or right bundle branch block.
   e. Left bundle branch block in standard leads, right bundle branch block in precordial leads.
10. Refractory ventricular tachyarrhythmias.

Indications For Pacing

Pacing should be instituted in all patients with anterior infarction and complete atrioventricular block or inferior infarction, complete atrioventricular block, and a ventricular rate less than 50. Patients with inferior infarction, narrow QRS complex, complete atrioventricular block and a ventricular response greater than 50 per minute can be observed in the absence of ventricular arrhythmias and evidence of hemodynamic embarrassment. The same guidelines can be used to determine the need for pacing in patients with inferior infarction and Mobitz I (Wenckebach) second degree atrioventricular block, with or without junctional escape beats. A more aggressive approach is warranted in patients with anterior infarction and intraventricular conduction disturbances because of the suddenness with which these patients may progress to complete atrioventricular block and asystole, and because even cases of acute, apparently "uncomplicated" left or right bundle branch block are in fact frequently cases of bilateral bundle branch block.[80] Therefore, we recommend the prophylactic insertion of a pacing catheter in patients with anterior infarction and Mobitz II second degree atrioventricular block, complete left bundle branch block, complete right bundle branch block with a QR pattern in lead V_1, or evidence of bilateral bundle branch block. Observation without placement of a pacing catheter is warranted only if the intraventricular conduction disturbance is known to have preceded the infarction. Unfortunately although pacing effectively prevents asystole, it does not appreciably reduce mortality when power failure is prominent as is frequently the case with an anterior wall infarction associated with right bundle branch block.[65]

In occasional patients, complete heart block persists after myocardial infarction so that permanent pacing is required. In others, particularly with anterior myocardial infarction, complete heart block is transient but left, right, or bilateral bundle branch block persists. Such patients appear to die suddenly with greater frequency than other survivors of acute myocardial infarction. Although the mechanism of these sudden deaths has not been documented, it is presumed that at least some of them are due to recurrent complete heart block and, therefore, might be prevented by prophylactic permanent pacing. In one series of patients, permanent pacing appeared to improve the long term prognosis of patients who survived myocardial infarction complicated by Mobitz II block.[93]

Temporary pacing should also be instituted in patients with bradycardias other than atrioventricular block (sinus bradycardia, sinus arrest, etc.) refractory to atropine when the rate is less than 45 per minute or there is congestive heart failure, hypotension, or ventricular irritability. In the last case, acceleration of the basic heart rate often abolishes the ectopic activity without additional therapy (see discussion of ventricular tachyarrhythmias). Because of the danger of further depression of atrioventricular conduction or spontaneous impulse formation, neither digitalis nor suppressant drugs should be given to a patient with bradycardia prior to the institution of pacing.

Although a detailed discussion of pacing techniques is beyond the scope of this review, a few points should be stressed. Pacing is safest in patients with acute myocardial infarction when demand or stand-by units

are employed. The stimulation threshold should be tested daily and the stimulus strength adjusted to not more than twice the measured threshold. Adequacy of sensing as well as pacing should be determined at the time of pacemaker insertion.[7]

Tachycardias

Tachycardias, like bradycardias, are detrimental in patients with acute myocardial infarction because they reduce cardiac output and coronary perfusion. In addition, accelerated ventricular rates augment myocardial oxygen requirements when the coronary circulation is already compromised. Treatment is directed at restoring sinus rhythm, although it is sometimes sufficient to slow the ventricular rate and await the spontaneous return of sinus rhythm.

Supraventricular Tachycardias

Atrial premature systoles usually require no therapy. If they are so frequent that cardiac output is compromised, quinidine is the preferred treatment. To achieve a therapeutic blood level promptly, quinidine should be administered orally or intramuscularly every 2 hours for 5 or 6 doses. If premature beats persist, the dose should be increased, ordinarily from 200 mg. the first day to 400 mg. the second day. If the arrhythmia is abolished, the patient is maintained on a daily dose of one half to two thirds the amount consumed the day the arrhythmia was controlled. Gastrointestinal symptoms, particularly diarrhea, often cause the interruption of therapy. One should attempt to control diarrhea with other medications before quinidine is discontinued.

Paroxysmal atrial and junctional tachycardias infrequently complicate acute myocardial infarction. If they cannot be terminated by vagal stimulating maneuvers such as carotid sinus massage or a vagomimetic drug such as edrophonium (10 mg. given as an intravenous bolus), a rapid-acting digitalis preparation should be injected intravenously (ouabain, initially 0.25 to 0.35 mg. with subsequent doses of 0.1 mg. every 30 minutes; or deslanoside, initially 0.8 mg., then 0.4 mg. after 1 hour and 0.2 mg. each hour thereafter) until sinus rhythm is restored or signs of toxicity supervene. Vagal maneuvers should be repeated before each subsequent dose of digitalis, since the vagotonic effect of digitalis may render the arrhythmia more responsive to vagal stimulation. Pressor agents should not be used to terminate the arrhythmia because of their tendency to cause more dangerous ventricular tachyarrhythmias. If tachycardia causes significant hypotension or left ventricular failure, immediate cardioversion is indicated with quinidine utilized as prophylaxis against recurrence.

The remaining varieties of supraventricular tachycardia often signify associated physiologic derangements, usually power failure. Therefore, the underlying problem must be treated as well as the arrhythmia. Sinus tachycardia, for example, rarely requires direct therapy. It is commonly observed during the second or third day after transmural infarc-

tion as a reflection of post infarction fever. When sustained, however, it often signifies extensive infarction with myocardial decompensation.

Multifocal atrial tachycardia (P waves of 3 or more different configurations) typically occurs in patients with chronic lung disease who are hypoxic and receiving bronchodilating drugs.[53] Digitalis and other antiarrhythmic medications are often ineffective, and the arrhythmia frequently subsides spontaneously when the patient's respiratory state is improved. Less often, multifocal atrial tachycardia presages the development of atrial fibrillation in patients who do not have lung disease.

After acute infarction atrial flutter and atrial fibrillation tend to be paroxysmal and frequently recurring arrhythmias, despite the use of antiarrhythmic drugs. Therefore, cardioversion is not indicated unless the clinical situation is desperate. Rapid atrial pacing (up to 600 per minute) appears to be as effective as D.C. shock in the treatment of atrial flutter (although this has been disputed by some authors)[74] and may be preferable since no anesthesia is required and the catheter can be left in the right atrium for future use.[49] Satisfactory rate control can generally be achieved with digitalis. Digitalis toxicity can usually be avoided if one remembers that complications such as fever, pulmonary congestion or infarction, hypoxia, etc., make it difficult or impossible to achieve a "normal" ventricular rate (i.e., 70 to 80 per minute). Until the complication is resolved, a ventricular rate of about 100 per minute may be the best one can hope for without "pushing" digitalis to toxic levels. Occasionally, uncomplicated atrial fibrillation with a rapid ventricular response cannot be slowed by digitalis alone. This is particularly true in recurring paroxysmal atrial fibrillation. In such cases, atrioventricular block can be augmented by propranolol (1 mg. given intravenously, repeated after 5 minutes to a total dose of 3 mg. or orally 5 to 40 mg. every 6 hours). Other beta-adrenergic blocking drugs such as sotalol, practalol and alprenolol may be preferable to propranolol because they may have less negative inotropic effect, but they have not yet been released for general use in this country.

Ventricular Tachyarrhythmias

Ventricular premature beats may be the forerunners of ventricular tachycardia or fibrillation. Early claims that virtually all primary ventricular fibrillation could be prevented by prompt treatment of ventricular premature beats[52] have been refuted by the observation that as many as 40 per cent of cases of ventricular fibrillation observed in a coronary care unit began with the first ventricular premature beats, or so soon after the first ventricular premature beats that there was insufficient time to administer antiarrhythmic therapy before the occurrence of cardiac arrest.[16] Another disturbing finding is that those ventricular premature beats occurring in the early post infarction period are less responsive to lidocaine.[20, 21] Different mechanisms of arrhythmia genesis are probably involved in early versus late post infarction arrhythmias, with reentry being the likely critical factor in early ventricular premature beats. Therefore, it is hazardous to extrapolate from the good effect of lidocaine observed relatively late in coronary care units to the prehospital situation. There is also an impression that lidocaine may not be efficacious in

abolishing potentially dangerous short coupled ventricular premature beats, but further work in this area is necessary.[61] Nevertheless, ventricular premature beats that are multifocal, occur in runs of 2 or more, fall on the T wave of the preceding beat, or exceed 5 per minute over several minutes of observation should be treated promptly and vigorously. Undoubtedly such treatment prevents many cases of ventricular fibrillation. Some studies have demonstrated a significant protective effect when lidocaine,[57] procainamide,[31] or bretylium[14] were employed prophylactically regardless of the presence of ectopic activity. However, the possibility of toxic side effects must be balanced against the potential benefits to patients who do not display ventricular arrhythmias.

The range of clinical manifestations of sustained ventricular tachyarrhythmias is great. At one extreme is slow ventricular tachycardia or accelerated idioventricular rhythm (rate 60 to 100 per minute), essentially an escape phenomenon occurring during sleep or periods of *relatively* slow sinus rhythm, usually subsiding spontaneously and not associated with hemodynamic disturbance.[75] Although treatment is usually unnecessary, slow ventricular tachycardia can be rapidly eliminated by atropine or lidocaine. At the other extreme are ventricular fibrillation and those ventricular tachycardias associated with circulatory arrest. These must be treated immediately with D.C. shock followed by lidocaine, then procainamide. Cardioversion is indicated when ventricular tachycardia is associated with severe hypotension or congestive failure, but ventricular tachycardia sometimes causes only minor hemodynamic derangement, and in those instances a trial of drug therapy is indicated before employing cardioversion. Some cases of ventricular tachycardia respond to such a low dose of D.C. shock that anesthesia is unnecessary. A blow to the chest ("thump-version") may sometimes restore sinus rhythm.[70]

Except for D.C. shock, the same modes of therapy are applicable to ventricular premature beats, ventricular tachycardia and ventricular fibrillation. However, intravenous procainamide, beta-adrenergic blocking drugs, bretylium tosylate, and pacemaker overdriving should be reserved for occasions when the gravity of the clinical situation justifies exposing the patient to the potential risks of such treatment. Lidocaine, because of its transient action and relatively slight hemodynamic effects, is the initial drug of choice when the basic heart rate exceeds 55 per minute. Treatment is initiated with an intravenous bolus (1 to 1.5 mg. per kg. of body weight) since a stable blood level may not be achieved for 1 to 5 hours if lidocaine is administered only by an intravenous infusion.[5, 24] Bolus doses can be repeated at 5 minute intervals. After the rhythm is stabilized, the drug is infused at a rate of 1 to 4 mg. per minute. At higher concentrations lidocaine causes hypotension and central nervous system symptoms including drowsiness, confusion, paresthesias, hallucinations, and convulsions. Toxic effects may be encountered even at normal infusion rates in the presence of congestive heart failure or hepatic insufficiency.

Procainamide should be given whether lidocaine is effective or not. In the former instance, lidocaine can generally be discontinued after a few hours. To achieve a rapid and stable blood level, the initial dose of procainamide should be 750 to 1000 mg. by mouth or intramuscularly,

followed by 250 to 500 mg. every 3 hours.[40] When there is greater urgency, procainamide can be injected intravenously. The infusion rate must be at least 50 mg. per minute and the electrocardiogram should be monitored for signs of cardiotoxicity (QRS widening of greater than 50 per cent). If hypotension occurs, a pressor agent such as norepinephrine should be administered while the procainamide infusion is continued.

Extracardiac factors that may contribute to ventricular irritability should be sought for and treated vigorously. These include hypoxia and electrolyte imbalance (particularly hypokalemia) owing to chronic lung disease, pulmonary congestion, emesis, diarrhea, and diuretic or corticosteroid therapy. Hypotension seriously impairs the effectiveness of antiarrhythmic drugs and must be treated. Occasionally, correction of hypotension, hypokalemia or acidosis suffices to terminate ventricular tachycardia. Untoward reactions from drugs such as digitalis, quinidine, thioridazine, and clofibrate[46] should be considered.

Quinidine is sometimes effective in controlling ventricular premature beats even when lidocaine and procainamide prove ineffective. Other drugs to be considered are digitalis (especially in the presence of a ventricular gallop or other signs of cardiac decompensation) and propranolol. Because of its negative inotropic properties, propranolol should be used cautiously, but it is noteworthy that in one study in which 34 patients with acute myocardial infarction and mild to moderate cardiac decompensation were treated with propranolol, there were no instances of increased congestive failure, the major side effect being sinus bradycardia.[47] Another advantage of beta-adrenergic blockade is that it reduces myocardial oxygen requirements and may help to prevent extension of the infarcted zone. Bretylium tosylate (300 mg. intramuscularly or intravenously diluted in 50 cc. 5 per cent dextrose in water and infused over 10 minutes) administered every 30 to 60 minutes until the arrhythmia is suppressed or until the systolic blood pressure falls below 100 mm. Hg may control otherwise intractable ventricular arrhythmias.[9] Bretylium is still considered experimental but its combination of positive inotropic, chronotropic and dromotropic effects is unique among antiarrhythmic drugs. Diphenylhydantoin is of little value in the treatment of ventricular arrhythmias other than those caused by digitalis.[90] Suppressive drugs may be used in combination when they are individually ineffective or to minimize side effects.

When suppressive drugs fail to control recurring ventricular arrhythmias, acceleration of the heart rate ("overdriving") is often effective. This is an empirical treatment, derived from the effectiveness of pacing in controlling ventricular tachycardia and ventricular fibrillation complicating complete heart block. Ventricular tachyarrhythmias are likely to occur when ventricular repolarization is asynchronous, and the degree of asynchrony is inversely related to the heart rate.[33] It is presumed that overdriving suppresses arrhythmias by rendering ventricular repolarization more synchronous.[23] Overdriving can be accomplished by drug-induced sinus tachycardia when pacing cannot be instituted immediately.[54] In such instances, atropine is injected intravenously. If the arrhythmias persist, isoproterenol is infused. Electrical pacing is preferable because of the greater precision with which the rate can be controlled. In either

case it is important to realize that overdriving is usually ineffective in terminating ventricular arrhythmias, the purpose of overdriving being to prevent recurrences. Sinus rhythm must be restored by other means before overdriving is begun. Overdriving should be initiated at a rate of 110 per minute, or at least 10 beats per minute faster than the basic heart rate. Often ventricular premature beats occur between the paroxysmal arrhythmias and their elimination is a convenient end point of therapy. If arrhythmias continue to recur, the pacing rate can be progressively increased until control is achieved or to the point of chest pain, signs of cardiac failure, or increased ventricular irritability. Simultaneous administration of suppressive drugs often permits arrhythmia control at lower pacing rates.[63]

POWER FAILURE

Congestive Heart Failure

Even the mildest forms of congestive heart failure should be treated since the failing heart maintains cardiac output at the expense of increased work. Frequent examination of the patient, searching particularly for ventricular gallop rhythm, fine pulmonary rales, hepatic engorgement, and jugular venous distention, as well as accurate daily weight measurements and daily, high quality portable chest x-rays, all aid in the early diagnosis of congestive heart failure.

A diuretic (mercuhydrin, 2 cc. intramuscularly, furosemide 40 to 80 mg. orally or intramuscularly, or ethacrynic acid, 50 to 100 mg. by mouth) should be given as initial therapy. The tendency of the latter two agents to cause hypokalemia is great and potassium supplementation or a potassium-sparing diuretic (spironolactone, 25 mg. 3 or 4 times daily; or triamterene, 100 mg. 2 or 3 times daily) should be given simultaneously. Furosemide and ethacrynic acid can be given intravenously in the same doses when very rapid treatment is needed.

If congestive failure is severe, or if diuretics alone are ineffective, digitalis is indicated. Digoxin by the oral or intramuscular route has a sufficiently rapid effect in most cases and maintenance therapy is easier than with the faster acting deslanoside or ouabain (for dosage, see discussion of atrial arrhythmias). Since a positive inotropic effect is achieved at less than a full digitalizing dose, it is unnecessary to push digitalis to toxicity to determine the maximum tolerable dose.

Additional modes of therapy may be required in the treatment of acute pulmonary edema. Morphine is valuable not only because it allays anxiety but because of its beneficial hemodynamic effects.[92] The patient should be placed in a sitting position, either in bed or chair. Oxygen therapy by nasal cannula or Venturi mask is indicated to correct hypoxemia.[60] Assisted ventilation may be needed if coexistent chronic lung disease or mental obtundation lead to hypoventilation and respiratory acidosis. A slow intravenous infusion of aminophyllin (500 to 750 mg. over 2 to 4 hours) helps relieve bronchospasm and potentiates other diuretics. Rotating tourniquets are particularly effective when coordinated by a timed, mechanical device (e.g., Jobst Automatic Rotating Tourniquet). When

these measures fail, phlebotomy may be employed. If the patient is anemic, simultaneous phlebotomy and transfusion of packed red blood cells effect both a reduction in the circulating blood volume and a rise in the hemoglobin level.

When severe congestive failure persists despite these measures, isoproterenol may provide an additional positive inotropic effect, and may also alleviate symptoms of circulatory overload by causing peripheral vasodilatation. Since positive inotropism is achieved with relatively small doses of isoproterenol (1 mg. of isoproterenol in 1000 cc. of 5 per cent dextrose in water, infused at a rate of 0.5 to 1 cc. per minute), the risk of precipitating arrhythmias is relatively small. Glucagon (3 to 5 mg. by intravenous bolus every 30 minutes, or 5 to 10 mg. per hour by intravenous infusion) may provide additional inotropic effect, but the effect is transient, and nausea, vomiting, and hypokalemia are frequent side effects.[68] Although recent papers have suggested that glucagon is best administered by prolonged intravenous infusion,[53, 91] caution is warranted since a report from the manufacturer indicates that in dogs prolonged glucagon infusion was sometimes associated with small hyaline pulmonary emboli.[19]

CARDIOGENIC SHOCK

Cardiogenic shock is the syndrome which results when cardiac output falls to levels inadequate for tissue perfusion. Since there is no simple test to determine the presence of underperfusion, shock is generally diagnosed on the basis of its clinical features such as systolic blood pressure less than 80 mm. of mercury, restlessness or depression of consciousness, oliguria (less than 20 cc. per hour) and signs of peripheral vasoconstriction.

Hemodynamic monitoring is essential for rational treatment of cardiogenic shock. Despite the inaccuracies of simple methods such as the sphygmomanometer (which generally underestimates the true blood pressure of patients in shock) and central venous pressure monitoring (which often fails to reflect hemodynamic disturbances involving the left ventricle), the complex instrumentation and frequent adjustment required for safe and accurate arterial, left ventricular, pulmonary artery, and pulmonary wedge pressure monitoring limits these techniques to research-oriented coronary care units.[10, 28] Catheterization of the urinary bladder and hourly measurement of urine volume permit an assessment of renal perfusion as an indirect measurement of cardiac output. Measurement of arterial blood gasses and pH helps estimate the extent of tissue hypoxia. Changes in measured parameters and clinical signs are used to evaluate the effects of therapy.

Treatment of cardiogenic shock begins with an accurate assessment of the clinical situation. Patients with hypotension and depression of consciousness caused by opiates or sedatives are not in cardiogenic shock, and generally require a minimum of supportive therapy until they recover spontaneously. Shock from pericardial tamponade is rare after myocardial infarction but may complicate post infarction pericarditis.

Treatment consists of pericardiocentesis, corticosteroids, and withholding anticoagulants. Volume-loading may be temporarily effective in maintaining cardiac output prior to pericardiocentesis.[89]

Signs of shock associated with a bradycardia or ectopic tachycardia may be reversed when the arrhythmia is corrected. When shock accompanies an arrhythmia it is often difficult to determine which disorder is primary. In such cases initial therapy should be directed at the arrhythmia since tachycardias can be terminated promptly by D.C. shock and bradycardias corrected by drugs or artificial pacing.

Hypovolemia is poorly tolerated when the cardiac output is already depressed by acute infarction. Hypovolemia may be caused by prior diuretic therapy, a strict low sodium diet, diaphoresis, emesis, diarrhea, and prolonged therapy with pressor agents, especially when fluid intake is poor because of nausea or anorexia. Although significant hypovolemia is present in only a minority of patients with shock after myocardial infarction, a high salvage rate can be obtained in this subgroup. Therefore, unless the patient in shock is also in pulmonary edema, a trial of volume expansion should be attempted. If the central venous pressure is less than 12 cm. of water, half normal saline in 5 per cent dextrose solution is infused at a rate of 20 ml. per minute and continued until there is satisfactory clinical response or the central venous pressure is 5 cm. above the initial reading. In the latter case, if the central venous pressure falls to within 2 cm. of the initial reading by the end of a 10 minute observation period, the infusion is resumed. If the initial central venous pressure is between 12 and 20 cm., a slower infusion rate (10 ml. per minute) is advisable.[85] Since several liters of fluid may be required to correct hypovolemia in some patients, volume-loading should not be abandoned unless signs of congestive failure supervene.

When fluid therapy fails to reverse the shock state, pressor agents are indicated. Metaraminol (100 to 200 mg. per liter of dextrose in water) or norepinephrine (8 to 16 mg. per liter of dextrose in water with 10 mg. phentolamine added to prevent sloughing in the event of extravasation) is the initial drug of choice, since the beta-adrenergic stimulating actions of these drugs enhance cardiac output, and their alpha-adrenergic effects help improve coronary perfusion by raising peripheral resistance. Because metaraminol acts primarily to stimulate release of endogenous norepinephrine, metaraminol becomes less effective when catecholamine stores have been depleted by its prolonged use, by chronic congestive heart failure, or by therapy with reserpine or guanethidine. Prolonged treatment with pressor drugs may cause hypovolemia, and fluid loading is sometimes necessary before patients can be successfully weaned off these drugs. The aim of pressor therapy is a systolic pressure of 80 to 90 mm. Hg unless significant hypertension had been present, in which case a systolic pressure of 100 to 110 mm. Hg is more appropriate. Additional increase of blood pressure merely augments cardiac work without further enhancing cardiac output or coronary perfusion.

Isoproterenol is effective in occasional patients in shock whose peripheral resistance is high. It can be used as the primary drug for patients with signs of shock who are normotensive or only slightly hypotensive. Its tendency to cause peripheral vasodilatation may cause an abrupt

decline in blood pressure. In other cases it may cause an increase in cuff pressure while actually resulting in a fall in aortic pressure. Finally, the propensity of isoproterenol to increase myocardial oxygen demand while it lowers coronary perfusion pressure may cause extension of infarction during isoproterenol administration. Digitalis, dopamine, and glucagon have also been advocated, as well as various combinations of drugs, but they have not been shown to increase survival.

Unfortunately most instances of shock following acute myocardial infarction result from myocardial dysfunction owing to extensive necrosis and ischemia, rather than from readily treatable causes such as hypovolemia and arrhythmia. Despite careful monitoring and judicious use of fluid loading and drug therapy, reported mortality figures in cardiogenic shock continue to range from 75 to 85 per cent. The median survival time was 10 hours in a series of 73 patients with shock after acute myocardial infarction, and all patients who failed to improve within 2 hours after the institution of drug therapy died.[78] The poor results of conventional therapy have led to the introduction of mechanical devices to assist the failing heart. The aim of these devices is to improve coronary perfusion by increasing diastolic pressure, to reduce cardiac work and oxygen requirements by diminishing central systolic pressure, and to improve organ function and reverse metabolic acidosis by augmenting forward aortic flow. The most widely used circulatory support systems are venoarterial pulsatile, partial bypass and intra-aortic balloon circulatory assist. The former is technically more difficult to use and requires an oxygenator as well as a synchronized pump, but the latter moves smaller volumes of blood and, therefore, may be less effective in severe shock.[11] Conceivably, early application of devices such as these may reduce the size of infarction and prevent the progressive myocardial necrosis characteristic of fatal cardiogenic shock. In a cooperative study, 87 patients with cardiogenic shock were treated with intra-aortic balloon counterpulsation. Although beneficial hemodynamic effects were generally accomplished, there was no significant improvement in patient mortality and only 8 patients were alive after 1 year.[79] Technical problems remain to be overcome, and while circulatory support systems offer promise for the future, they are still experimental and not generally available.

SURGERY

Elective surgical correction of the sequelae of myocardial infarction may be indicated when heart failure or arrhythmias refractory to medical therapy are due to correctable lesions. Occasionally, emergency surgery is justified as a desperate measure in critically ill patients despite the high operative risk when the outlook seems otherwise hopeless.

Among the candidates for emergency surgery are patients with cardiogenic shock persisting after several hours of medical therapy, with uncontrollable ventricular tachyarrhythmias or cardiac arrest, patients unable to be weaned off of assisted circulatory devices, or patients who

sustain an acute infarction during a cardiac surgical procedure. Although dramatic surgical successes have been described, these generally have been single case reports or small uncontrolled series.[61] Prerequisites for surgery are coronary arteriography, ventricular angiography, and cardiac catheterization. Therefore, there must be adequate diagnostic facilities available when surgery is contemplated. If necessary these may be performed during cardiac bypass.

Acute mitral regurgitation owing to papillary muscle rupture is a potentially correctable condition. The manifestations of papillary muscle dysfunction after infarction range from the systolic murmur heard in the majority of patients[35] to acute severe left ventricular failure secondary to rupture.[15] Patients with papillary muscle dysfunction are generally less severely ill than those with rupture although acute severe mitral regurgitation without rupture may occur occasionally. When severe mitral regurgitation develops suddenly, the normal left atrium transmits increased pressure to the pulmonary bed and pulmonary edema ensues.

Perforation of the ventricular septum may be difficult to distinguish from the papillary muscle disorders on clinical grounds, since both may cause loud, holosystolic murmurs. However, the presence of a thrill favors the diagnosis of septal rupture. Although patients with septal defects may deteriorate suddenly, they can generally be stabilized with medical therapy so that a patient with shock, congestive failure, and a systolic murmur who survives longer than 2 days probably has a perforated septum rather than papillary muscle rupture.[82] Perforation of the septum occurs in about 1 to 2 per cent of infarctions, generally within the first few days. By the end of 2 months the mortality rate approaches 80 per cent. Surgical repair is the definitive treatment but should be deferred several weeks if possible to permit healing of the infarction and reduce the likelihood of suture disruption. Successful early repairs have been reported when the clinical condition did not stabilize on medical therapy. About 35 per cent of patients with septal rupture have associated ventricular aneurysms, so that combined surgical procedures may be necessary.

If left ventricular angiography demonstrates a localized area of akinesis or aneurysm and the remainder of the ventricle appears to function adequately, resection may improve left ventricular function.[31] If greater than 35 per cent of the left ventricle must be resected, infarctectomy is likely to cause further deterioration of left ventricular efficiency.[89] Occasionally, however, apparently moribund patients have successfully survived emergency aneurysmectomy.[62]

Although saphenous vein or internal mammary artery bypass grafts have been advocated for progressive or preinfarction angina,[15] the results of this procedure when performed immediately after infarction have been generally disappointing. One group, however, claimed success in 6 of 7 patients who had bypass grafts performed within 12 hours of acute infarction.[77] All had had recent arteriograms so that the coronary anatomy was known. The one patient who was in shock preoperatively succumbed. The other 6 patients had been clinically "unstable" and surgery was performed in an effort to prevent extension of infarction and devel-

opment of the shock state. It is not clear, however, whether these patients might not have done as well with conventional medical therapy. One active surgical group described good results, with overall early mortality of 5.6 per cent in 571 patients with impending myocardial infarction and 32 patients shortly after infarction.[8] Others, however, advise waiting at least a month after infarction before performing coronary artery bypass and have reported 50 per cent mortality of those operated in the first week after infarction.[13]

CONCLUSIONS

We have attempted to review the current state of the art of treatment of myocardial infarction from the standpoint of the clinician. Although many aspects of acute coronary care are relatively uncontroversial, this remains a rapidly changing field and the reader should be fully cognizant that recent experimental work, if confirmed, may necessitate modifications of some of the guidelines presented here. Among the more important unresolved issues relating to therapy are the following:

1. What will be the impact on mortality of mobile coronary care units and prehospital intervention?
2. Is sinus bradycardia protective or is it more likely to provoke ventricular irritability?
3. Can a practical distinction be made between "benign" and "malignant" ventricular premature beats (i.e., those with a short coupling interval having, at least in dogs, a much greater potential for the initiation of ventricular tachycardia and fibrillation)? If so, are atropine or lidocaine effective in suppressing the "malignant" ventricular premature beats?
4. Is the prophylactic use of antiarrhythmic drugs warranted prior to documentation of arrhythmias?
5. When and how should persistent ventricular premature beats be managed during the post hospital phase?
6. Should alpha or beta blocking agents be employed soon after the onset of acute infarction in an effort to minimize infarct size? Similarly, should positive inotropic agents such as digitalis be avoided in the early stages of infarction?
7. When should invasive methods such as mechanical support systems and coronary bypass surgery be initiated? Can valid controlled studies be devised to confirm the efficacy of these exciting new techniques versus traditional conservative medical management?

These are but a few of the vexing, but highly relevant problems that hopefully will be resolved in the near future. Ultimately, greater understanding of the pathogenesis of ischemic heart disease will be necessary in order to permit the development of effective measures for the prevention of myocardial infarction.

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